STATE OF MINNESOTA DISTRICT COURT
COUNTY OF RAMSEY SECOND JUDICIAL DISTRICT

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The State of Minnesota,
by Hubert H. Humphrey, III,
its attorney general,
and
Blue Cross and Blue Shield
of Minnesota,

Plaintiffs,

vs. File No. C1-94-8565

Philip Morris Incorporated, R.J. Reynolds Tobacco Company, Brown & Williamson Tobacco Corporation, B.A.T. Industries P.L.C., Lorillard Tobacco Company, The American Tobacco Company, Liggett Group, Inc., The Council for Tobacco Research-U.S.A., Inc., and The Tobacco Institute, Inc.,

Defendants.

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TRANSCRIPT OF PROCEEDINGS
VOLUME 7, PAGES 1169 - 1362
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P R O C E E D I N G S.

THE CLERK: All rise. Ramsey County District Court is now in session, the Honorable Kenneth J. Fitzpatrick now presiding.

Please be seated.

THE COURT: Good morning.

(Collective "Good morning.")

THE COURT: We have a motion to admit pro hac vice Marie V. Santacroce. Is she here?

MS. SANTACROCE: Yes, Your Honor.

THE COURT: Welcome to Minnesota. And the motion is granted.

Mr. Ciresi.

MR. CIRESI: Yes, Your Honor.

Your Honor, yesterday Mr. Bernick in his opening statement made the following statements: "Did we use private facts for this discussion in our positions, or were we relying on the same public facts that everybody else has made available to them through the offices of the scientific community and the Surgeon General? Our position is that our views and our conduct was driven by public facts that our customers, that the states and others can appreciate just along with us." Page 1117 of the transcript.

Again at page 1118, "How do we reconcile what we

said in our positions with our responsibilities to our customers to share information with them? We relied upon the fact -- and it will be a fact -- that

we're dealing with a public discussion and public facts. We expected our customers to do what everybody else and the public did, which is to see what the public facts were, the public decisions were, and the debate, and to make their own decisions about what opinions to hold. It comes down to making a choice based on publicly available information."

We believe that that is a representative admission by Mr. Bernick on behalf of all of the defendants that they did not disclose their private information which was in their files, and that the jury should be so instructed that the defendants have not disclosed private information with regard to the undertaking that they undertook in 1954.

MR. BERNICK: Your Honor, Mr. Ciresi I don't think began at the beginning of that portion of the argument and he's taken those statements out of context. I stand by the statements that were made, but what I was describing to the jury -- the first part of the opening statement explored in detail the fact that the information that Mr. Ciresi showed from our files on opening and characterized as being

private information, known to nobody else, that those representations were wrong because the same theories, the same basic principles that are in our documents were in the open scientific literature, indeed in large part they came to us from the open scientific literature. That's -- that's an argument that we made, we stand by, and the jury can assess at the conclusion of the case after they hear the evidence.

I then went on to talk about what our defense of smoking had been, that was the very last segment, and I described to the jury the positions that we had taken publicly as part of our public defense of our position, and the message was very, very simple, which is when it comes to causation or it comes to addiction, we erected our position on the basis of those public facts because the debate was in fact a public debate. Essentially, we participated in it.

There was no representation, there was no admission that there were private facts that were in some fashion material that we had failed to disclose. All that I was saying, and I think it was clear to the jury, was that we jumped into that public debate and we participated in it like anybody else, and our responsibilities to our consumers were discharged in the same fashion that they would be under the same

circumstances, which is consumers, cognizant of that same public debate, could form their own opinion. I think it's a perfectly straightforward argument, it's an important part of the case, and there's absolutely no admission involved in that. The jury can draw their own conclusions, Your Honor.

THE COURT: Well what may have been clear to the jury is not exactly clear to the court. In

reading the transcript, it does appear that -- I'd have to go back and read the entire transcript, I guess, but from these statements, is it correct that you are not relying solely on what was publicly available?

MR. BERNICK: For purposes of the positions that we announced on causation and addiction, we were relying upon -- we were reciting the same public facts that were available to everybody; for example, mechanism for causation of cancer has not been established, that's something that we can show from the scientific literature. The failure to replicate human-type lung cancer in significant numbers and consistently, that's in the Surgeon General's report in 1982. Those are the kinds of facts, Your Honor, that we relied upon and still do rely upon in our articulating our position on causation.

THE COURT: Exclusively?

MR. BERNICK: I would suppose for purposes of our public positions we would rely upon public facts, yes.

We don't believe that there's anything that's inconsistent with that that we have in our own files, but all that I was saying is that when it comes to a public debate in Washington, we're jumping in and using the same facts everybody else does. They're not -- they're not unknown facts, they're known to everybody.

It's really a different -- it's a very different issue, Your Honor, from the issue whether there was something that was in our files that nobody else knew. That's what I stressed in the opening part -- in the bulk of my opening statements. Was there some secret that we had? And -- and we'll say that we didn't have a secret. There was no silver bullet that we had discovered internally that we failed to share with people, and they won't be able to show it either.

THE COURT: But the issue is -- is not the issue whether or not you agreed to do independent research to examine the hazards of smoking?

MR. BERNICK: Yes, there's an independent

issue whether we agreed to do the research. The front part of my opening statement I said we did agree to do the research, and it's right in the Frank Statement, and we went ahead and satisfied that promise and satisfied that obligation.

THE COURT: And are you relying on that research?

MR. BERNICK: We're relying --

Research that we agreed to do in the Frank Statement was the CTR grant program. We are relying upon that research, Your Honor, in saying that we discharged the obligation of the Frank Statement.

Again, we said the Frank Statement was there,

the Frank Statement said that we'd set up a research organization and we would fund it and we would make the research available. That's exactly what the CTR grant program was. We did it. We made the research available. We are relying upon that public research in saying we discharged the obligation that was assumed in the Frank Statement. That's absolutely correct.

Now there's other research that we did, Your Honor, that was research that was commercial research, research that was directed to changing our product. Some of that research was published, some

of it was not because it might not be of publishable quality or it might be proprietary. That's a totally different ball of wax. That's research that we used commercially to change our product. Got Ames test, inhalation tests. All companies do commercial research.

We never undertook, if this is the force of Your Honor's question, which I would like very much to respond to, we never undertook to make available to the public every piece of research data that we ever produced internally. We have made no such commitment. We do not construe the Frank Statement in that fashion.

I didn't argue to the jury that the Frank Statement undertook that obligation. The Frank Statement was a -- is a commitment to create a certain research program through outside scientists. That was done. Commercially we engaged in other research. That research also was done. But we don't sit there and, every time we finish a commercial research project, turn it over to, you know, the Surgeon General or to the New York Times. That's not how companies do business.

I'm trying to be responsive to Your Honor's question. I'm not sure if I have been.

THE COURT: Okay. My concern is -- and I understand what you're saying, that you didn't agree internally to do everything, but on the other hand you are saying here that you relied on none of your private research in taking a position. That's what I'm concerned about.

MR. BERNICK: Okay. Well let me rectify that.

THE COURT: All right.

MR. BERNICK: There's been a lot of discussion about the public positions we've taken and all the guys standing up under oath and saying I don't think nicotine is addictive or people saying causation has not been established. Those are public positions. When we're asked for our views, we state a public view.

What I told the jury was when it comes to a position like causation, that's a position which we

have articulated and which we rely upon public facts. We don't rely upon our commercial research to take a position on whether cigarettes cause disease. The two things don't have much to do with one another. We rely on the public research that's published in peer review journals or in the Surgeon General's report, as an example. What happened in the

laboratory experiments, that's a publicly stated fact; it is one of the pillars of our public position on causation. Same thing with regard to addiction. You're talking in the world of what we say about causation and addiction, Your Honor, about matters that have great importance for regulatory purposes, for legislative purposes, for litigation purposes. Those are statements that are made in the public arena.

We, in creating those positions, used the same facts as everybody else did. It's just a very -- it's like you were thinking about, what is it that you would say to a regulator? We say, well, we'll work with the same information everybody else has. This is our position. That's what I was telling the jury.

THE COURT: I'll take the matter under advisement.

MR. CIRESI: Your Honor, may I just address two things?

THE COURT: I don't want to spend the morning on this.

MR. CIRESI: And I don't either.

THE COURT: Okay.

MR. CIRESI: First of all, when they

referred to the Frank Statement, they also said as follows, "The joint financial aid will, of course, be in addition to what is already being contributed by individual companies."

Now, Mr. Bernick's position is very simple. Whatever is in the public, we will take a position based only on that information. Now let's just think about that for a minute. If that is the legal duty -- and this is a legal issue -- then I as a manufacturer can have within my files a plethora of information regarding the dangers and hazards which contradicts, supplements, changes or modifies what is in the public domain, and I don't have to say anything. I'll just take a public position based on what's out there. Totally contrary to the law and totally contrary to the undertaking that they took in the Frank Statement, because they divided -- they talk about the Scientific Advisory Board of the TIRC, actually they talked about TIRC, and they talk about the fact that they are doing research in addition to that in the individual companies. All of that has to be disclosed. That's absolutely essential. And it is contrary to the law to say that I can sit back

and -- let me quote Mr. Bernick -- "Listen to our positions carefully. They were carefully crafted."

Yes, they were carefully crafted. And this is their position: We're only doing what's in the public, and anything that's in our files has nothing to do with positions we took. That's simply contrary to the law, and we believe we're entitled to an instruction on that.

MR. BERNICK: If we made representations to the public which are in fact contradicted by what's in our own files, Mr. Ciresi can prove it up to the jury. The whole force of my opening statement for an hour and a half was that he won't be able to do it. That's the issue for the jury to resolve. I'm not saying we can sit there and make public statements with impunity for what's in our files. If in fact we have material information in our files and people should have known, we failed to disclose it, we issued contrary public statements and he can prove it up, the jury will be convinced and they can find against us, if there's any evidence that had any impact on people who are plaintiffs here. He won't be able to do that. But it has nothing to do --

What I made was a very simple statement to the jury. We participated in the public debate using the same materials as everybody else did. That's not an admission that somehow we should have disclosed more.

If he thinks that we should have, that's exactly what he can pursue.

And with regard to the Frank Statement, that's in addition to what's already being contributed. Some of the companies already were funding outside research with independent scientists; for example, at the Medical College of Virginia. And that continued. That's not a statement that somehow all of a sudden by making the Frank Statement, we now open the door to all of our proprietary research and say anybody can come in and take a look at what we're doing with our product. That way we couldn't conduct business.

These are all issues of fact, Your Honor, for the jury to resolve. I think we were straight with the jury. If we weren't straight with the jury, they're going -- they're going to let us know that in their verdict. But these are matters for the jury to resolve.

THE COURT: Well --

MR. BERNICK: I'm not making any arguments about Mr. Ciresi's opening statement. We could have a long discussion about what he led the jury to believe in his opening statement.

THE COURT: All right. Let's see how it works out. But I am concerned. Maybe I don't

understand what you said and maybe the jury does, but I am somewhat concerned. And as the case unfolds, if in fact the defendants do take the position that their private research is not relevant to their public positions, then you probably will find my instructing the jury to the contrary. So you may want to keep that in mind.

Why don't we move on, huh? Okay. Bring the jury in.

(Jury enters the courtroom.)

THE CLERK: Please be seated.

THE COURT: Good morning, members of the jury.

(Collective "Good morning.")

THE COURT: Mr. Ciresi.

MR. CIRESI: Thank you, Your Honor. The plaintiffs called Dr. Richard D. Hurt to the stand. Doctor.

THE CLERK: Please remain standing and raise your right hand.

(Witness sworn.)

THE CLERK: Please state your name for the record.

THE WITNESS: Richard D. Hurt.

THE CLERK: Thank you. Please have a seat.

RICHARD D. HURT

called as a witness, being first duly sworn, was examined and testified as follows:

DIRECT EXAMINATION

BY MR. CIRESI:

Q. Good morning, doctor.

A. Good morning.

Q. Let me start out with a little personal information for the jury so they have an understanding of where you came from and -- and what you do in your profession.

Can you tell us where you live, sir?

A. I live in [DELETED].

Q. Are you married?

A. I am.

Q. Any children?

A. I have three children and two grandchildren, one just a week and a half old.

Q. All right. Can you tell us what your present employment is?

A. I'm a consultant in internal medicine and director of the Nicotine Dependence Center at the Mayo Clinic.

Q. Doctor, can you maybe get that mike up a little

bit and make sure everybody --

Is everybody able to hear?

A. Is that okay? Is that better?

Q. How long have you been at the Mayo Clinic?

A. I came there in 1973, so 28 -- 26 years I guess, almost 26 years.
Q. And you're a professor of medicine at the Mayo Medical School?
A. That's correct.
Q. Okay. And you consult on internal medicine at the present time?
A. That's right. That's the title, is consultant. It's really a staff member of the Mayo Clinic, is the better -- better title to use.
Q. Can you describe what your duties and responsibility are in that regard, doctor?
A. I'm a primary-care internist. I see patients every day. A primary-care internist is like a family physician, although I'm an internal medical physician. I see adults, no pediatrics and no obstetrics. So that's kind of one side of my job is to see patients on a regular basis.
Q. Okay. And where were you born, sir?
A. In Murray, Kentucky.
Q. And where did you obtain your undergraduate

degree?
A. Right -- right at home Murray State University of Murray, Kentucky.
Q. Was that in 1966?
A. That is correct.
Q. Okay. And where did you obtain your M.D. degree?
A. From the University of Louisville in Louisville, Kentucky.
Q. After obtaining your degree did you have an internship?
A. I did. I went to the Baptist Hospital in Memphis, Tennessee, and did my internship there in internal medicine.
Q. After you completed your internship at Baptist Memorial, what did you do?
A. I got drafted and I was in the Army for two years. And then after that I -- I came to Mayo Clinic to do my fellowship.
Q. So you were in the Army from 1971 to '73?
A. That's correct.
Q. Now the fellowship at the Mayo Clinic between 1973 and 1976, can you describe that, please?
A. Well a fellowship in internal medicine, we go through rotations, various subjects in internal

medicine like hematology and cardiology and those sorts of things. At that time we had a required rotation in psychiatry, and that's where part of my interest in this whole area came from. My first rotation was on the addictions unit at Mayo Clinic, at the time when addictions units were very uncommon, in fact it was just opened a year and a half or so before I did my first rotation.
So in the fellowship you rotate through various

stages of -- of medicine or various topics in medicine like those, so in those three years I rotated through probably ten or 12 of the areas of internal medicine.
Q. And in 1988 you became in charge of the Nicotine Dependence Center?
A. That's correct. That was after a two-year planning effort to develop this program, which was started in April of 1988.
Q. Can you tell us what the Nicotine Dependence Center is at the Mayo Clinic?
A. It is a program that's based on all that we can learn and know about the treatment of patients with nicotine dependence. It's solely devoted to that. It's modeled after an addictions model which obviously came from all the things that I'd learned

from before, and the counselors are trained -- the counselors are the ones who provide most of the services, although I oversee that along with other physicians who work in the Nicotine Dependence Center -- the counselors provide services to the patients what are for the most part referred by Mayo physicians, but some are self-referred. About 85 percent of the patients are referred by Mayo physicians who may be concerned about the patient, may be concerned about their heart disease or their lung disease and want them to try to stop smoking, and the other 15 percent or so are referred by themselves. They call up and make an appointment to see one of the counselors.
The counselors are master's level people who have training in what we consider to be kind of the pillars of this program, which is behavioral treatment, addictions treatment, pharmacologic treatment, and prevention of relapse. Those are kind of the four hallmarks or the pillars of this program.
Q. And how many patients have been through the dependence center since 1988, doctor?
A. Since April of 1988 they have seen 15,313. That was as of December of 1997.
Q. In addition to patient services, is there

research and education conducted at the Nicotine Dependence Center?
A. Correct. And the Mayo logo, which we all really try to adhere is a best we can, has three parts to it, it's three interlocking shields, and the middle one is patient services. We really focus on patient care, that's our focus in the entire institution, but it's really also the focus within the Nicotine Dependence Center. So the center of our activities has to do with the patient, what's in the best interests of the patient is in our own best interest.
The other two interlocking shields are research and education. We view this as an integrated practice of those three things, that's what makes

Mayo Clinic really special because we have those three things operational all the time in all the things that we do.

The analogy is a tricycle. A tricycle has three wheels. The big wheel in the front is the driving force behind the tricycle, but the tricycle obviously will not roll unless all three wheels are present. So the big wheel in the front is patient services, and the two wheels in the back are education and research. And one of our goals at the very beginning of this was to establish the program so that it had

all three of those things almost from the very beginning. So we opened up our clinical program in April of 1988 and did our first nicotine patch study in September of the same year and began having our first medical students and residents rotate through the Nicotine Dependence Center within the first year.

So it was the -- it's the integration of those three elements that really make what we do there very special.

Q. Doctor, I'd like to go over some of your -- your qualifications and background, some of the organizations that you belong to and have belonged to during the course of your career. You've been a member of the District Chemical Abuse Advisory Committee?

A. Correct.

Q. You've been a member of the Mayor's Advisory Committee on Alcohol and Drug Abuse and also served as chair of that committee at one time?

A. That's been a while ago, but I did that.

Q. Okay. And you've also served for the Smoke Free Generation Minnesota vice chair and board of directors?

A. Correct.

Q. You've also been on the Rochester Foundation for

Educational Excellence?

A. That's correct.

Q. You've also been a member of the American Foundation -- I'm sorry, American Society of Addiction Medicine Committee on Nicotine Dependence?

A. And that's really our national organization that has to do with addiction medicine. It's a national organization made up of 3,500 or 4,000 physicians from around the country. That's -- that's really kind of the -- the main focus of our national activities.

Q. And you serve as chair of that organization?

A. I serve as chair of the conference committee. They've put on a conference and have put on 11 or 10 conferences now on nicotine dependence. The first one was here ten years ago and the 10th one was here just this last year.

Q. You've also served on the board of advisors of the Indiana University Nicotine Dependence Center

from 1992 to the present time?
A. Correct.
Q. You've also been a special consultant to the Ministry of Health in Singapore?
A. Correct.
Q. And you've been a special consultant to

the -- and I know I'm going to torture this word -- Bekhterev --
A. Bekhterev, yeah.
Q. -- Psychiatric Institute in St. Petersburg, Russia?
A. Right. That was a humanitarian aid commission that I did through AmeriCares, going there to teach them about nicotine dependence and teaching them how to learn -- or teaching them about using nicotine patch therapy, which they had not had up until that time.
Q. You've also served on the Society of the Research on Nicotine and Tobacco?
A. Correct.
Q. And you've been a member of the AMA Adolescent Smoking Cessation Advisory Board from 1995 to the present time?
A. Yes.
Q. You've also been a member of AmeriCares Medical Advisory Board from 1995 to the present time?
A. Correct.
Q. You're also a member of the American College of Physicians and hold a fellowship position there?
A. Uh-huh.
Q. And you're member of the American Society of

Addiction Medicine.
A. Correct.
Q. Okay. Now you've also published a number of articles in peer-review journals; is that correct, doctor?
A. That's right, yes.
Q. And I think it's in excess of 60 articles in peer-review journals, plus also chapters in books?
A. Correct.
Q. Okay. I'd like to go over just a few of those with you so the jury gets an understanding of the nature of the work that you've done in this area.
You published in the Mayo Clinic's Proceedings an article entitled "Long-term Follow-up of Persons Attending a Community-Based Smoking Cessation Program;" is that correct?
A. That's correct.
Q. You can you describe that article just briefly?
A. In the mid-1970s there were very few treatment facilities available for patients or for even people from the community, and there was a -- a community effort called The Smokers Clinic which was run three times a year, available at Rochester Methodist Hospital, and it was a program that was run over an

eighth-week period of time, and one session each week for those eight weeks. And this study he's mentioning is the outcome from that. We looked back at the people that had been part of that study over time and then determined what -- how well they did as far as how well they were able to stop smoking as a result of that. That's one of the first -- first ones that we did as far as doing smoking outcomes.

Q. Another article you published was in what's called JAMA, or the Journal of the American Medical Association, in 1989, "The Making of a Smoke-Free Medical Center?"

A. Correct.

Q. Can you describe that one, please.

A. Well in the mid-'80s there was a move afoot within the medical communities around the country to develop a smoke-free indoor-air policy. We had patients who were concerned about inhaling other people's smoke because they would be in the hospital and within the clinic, they might have lung disease or heart disease, so it became an issue that -- that the institution, the Mayo Clinic, decided to implement a smoke-free policy throughout the buildings, on the grounds and so on, and this was an article that -- that really described the process. We were probably the second medical center of any

size to do this, and this described the process. And other people around the country then used that process on how to go about doing this to implement it in other -- other -- other institutions. And eventually that became a national policy that's been mandated by the JCHO for all hospitals within -- within the country.

Q. What was that acronym you just used?

A. JCHO, the Joint Commission on Health-Care Organizations. It's the accrediting body. They come in and determine whether or not your hospital is clean, safe, and all the procedures are being done. So it's the thing that gives accreditation for hospitals. So that's a requirement from that organization for all hospitals throughout the country now.

Q. Another article that you published was entitled "The Inhalation Treatment of Severe Nicotine Dependence," and that was published in the Mayo clinical Proceedings Journal. Can you describe that one briefly?

A. Well when we were approved to start our nicotine dependence program, we proposed actually to have several different levels of intervention or levels of treatment. We knew that people with more severe

nicotine dependence would need more intervention. We didn't know exactly at that time what kind of intervention they might need, and so when we -- we got approval from the institution to -- to start this program, they recommended that we -- before we go to more intensive interventions, that we do a research project to, one, prove that we could actually do it, provide a more intensive intervention, and two, that anyone would come to sign up for more intensive intervention.

And this article has to do with the inpatient treatment program for patients with severe nicotine dependence, people who had tried to stop smoking in every other way that they could do, or may have had very severe medical complications, may have had emphysema or peripheral vascular disease, hardening of the arteries or other conditions and were unable to stop smoking despite having that. So this project was to see if people would check into a hospital, basically, like other people would check into a hospital for treatment of their other addictions like cocaine or alcohol or opiates or other addictions. And we had people to come for this.

And that article actually describes the program,

describes the outcome. And the outcome, though it was good, it was less than we liked for it to be. I think around 28 or so percent of the people that came to that program were able to stop smoking and maintain that abstinence even though they were hospitalized for two weeks and received everything that we could provide for them. So these people were really severely ill with a severe degree of dependence.

Q. Another article, doctor, is entitled "Serum Nicotine and Cotinine Levels During Nicotine Patch Therapy" which was published in the peer review article Clinical Pharmacology and Therapeutics. Can you briefly describe that article?

A. Well that actually had to do with this -- this project we just talked about where the people were in the hospital for a period of two weeks and we would draw their blood every day to see how much nicotine was in their blood. And cotinine is the other thing that -- that he mentioned. Cotinine is a metabolic product of nicotine and it's easily measured in the blood or even the saliva or the urine of a person who is using nicotine replacement therapy or is a smoker.

So we measured the levels when they were smoking their usual amount of cigarettes to get an idea of

what their baseline level was, and then we measured the level every day while they were in this smoke-free, intensive inpatient treatment for their dependence. And they compared the levels. And so what we found was that at the time that they were

smoking their usual number of cigarettes, their level was about here, and we put them on a single-dose nicotine patch which delivers 22 milligrams of nicotine per day, and we looked at the blood levels while they were in the unit. The blood levels were about half of what they were when they were smoking their usual number of cigarettes.

And we concluded that we were probably underdosing a fairly large number of people if we only gave them one nicotine patch. So it was a way of looking at this and doing a -- a fairly sophisticated study of -- of pharmacologic therapy, but determining what -- what they had to begin with and what they were on a single-dose patch.

The analogy I guess I would se would be -- or what we found was that one patch does not fit all smokers because some have higher levels, higher levels of dependence. It would be like a person with diabetes. Every -- every diabetic would get the same dose of insulin, and it just doesn't work that way.

We have to individualize the treatment.

Q. Doctor, there was another article published in JAMA which was entitled "Nicotine Patch Therapy for Smoking Cessation Combined with Physician Advice and Nurse Follow-up: One-year Outcome in Percentage Nicotine Replacement." Was that part of the same program?

A. No. This was a different study. This was a very large study that we did in three -- three different places actually, Mayo Clinic Scottsdale, Mayo Clinic Jacksonville and Mayo Clinic Rochester. We had several hundred patients in this study and we did the same thing again, but we did -- we measured their levels while they were in their free state, smoking their usual number of cigarettes, but then they just received advice from the physician and follow-up by a nurse. They weren't in the hospital for inpatient treatment, they were in their free-living state to see what happened as far as the outcome, how well they were able to do as far as stopping smoking, but also to try to figure out what the percentage of replacement is. If their level was this at the beginning, what kind of legal did they have when they were on the nicotine patch.

Q. Okay. Another article that was published in the

Alcohol Clinical Experience and Research Journal is entitled "Nicotine Dependence Treatment During Inpatient Treatment for Other Addictions: A Prospective Intervention Trial." First of all, what's a prospective intervention trial?

A. Well there -- there are kind of two types of studies. One is prospective, where you figure out ahead of time what you're going to study so that you can collect the information and you end up with better information because you don't have missing

information. So prospective means that we thought ahead of time what we were going to do before we recruited the patients to go into this study.

A retrospective study is something that's happened in -- that's already happened in the past and we're looking back into the past to see what happened with -- with the patients.

The first study Mr. Ciresi mentioned of The Smokers Clinic was a retrospective study. We looked backwards in time to see what happened to the people and to figure out how -- how well they did with The Smokers Clinic intervention. So a prospective study is generally thought of as being more scientifically sound because you're able to figure out what you want to collect before you actually start the study.

Q. Are those two types of what are called clinical trials?

A. Well a clinical trial would be where there's a medication involved or a drug involved, and those would be prospective, but they would be randomized clinical trials, "randomized" meaning the assignment to the drug or to the placebo is done at random, by chance. And "double blind" meaning I don't know what you're taking and you don't know what you're saying, so that we can be fair in the assessment of that, so we don't do something more for the people who are receiving the drug as opposed to those that are receiving the plabebo. So I'm blinded to it, our staff is blinded to it, and the patients are blinded to it, so that we get a very good assessment of the effect of drug.

Q. Can you tell us, then, what the article -- or the study was about in the Alcohol Clinical Experience and Research?

A. This is actually one of the very first articles that -- that looked at the issue of treatment of nicotine dependence in people with other addictions. Up until that time the treatment community, if you will, that -- that encompasses all of the addictions treatment field, had embraced all the other

addictions, but nicotine dependence was kind of left out of -- out of the equation, and up until the early 1990s smoking was still allowed in the addictions unit at our place and in most places around the country, because there was a fear that if you tried to help people stop smoking at the same time they were going through their other addictions treatment, maybe for cocaine and alcohol or other -- other drugs, the fear was that if you treated their nicotine addiction at the same time, that you might have an adverse effect on the treatment of the other drugs.

And -- and so we did this study to see if we could provide an intervention for patients that were undergoing treatment for their other addictions at

the same time. And what we found out was that we could do that, and that though it was modest, there was a success rate that was better for those that received the intervention compared to those who did not.

And then the third thing is that even though they may have received intervention for the nicotine dependence, that did not make them relapse to alcohol use or other drug use in a higher rate than you would expect from the control group. So it was really one

of the first studies to address the issue of the seriousness of nicotine dependence in people with other addictions.

Q. Doctor, another article that was published in 1995, again in JAMA, was "High-Dose Nicotine Patch Therapy: Percent Replacement in Smoking Cessation."" Can you briefly describe that study.

A. That really fits into kind of the train of research that we were doing. In the initial work we found out that the levels that the people had when they were smoking were higher than we would ever be able to achieve with a single-dose patch, so this study actually -- we put people in the hospital again, measured their blood levels and urine levels when they were in their free-living status and then put them in the hospital for an intensive inpatient treatment program, measured their blood levels twice a day, collected all their urine, collected all kinds of other specimens and samples, and then also gave them treatment for their -- their nicotine dependence at the same time. And this one was different because instead of giving one patch at a time, we gave two patches. But it was blinded, it was randomized and it was controlled, so some people got two patches, two active patches, and some people got one active

patch, regular size, and some people got a small active patch and some people got a placebo. Everybody wore three patches at a time, so we didn't know what they had, they didn't know what they had, and measured the levels and we found with the higher dose levels that we could get better replacement, as you would expect, get higher levels that came closer to what they had when they were in their free-living state and smoking their usual number of cigarettes, and those that received lower doses had lower levels.

And then the second part to that is the outcome, who did better as far as stopping smoking? And as you'd expect, the people that had higher doses, higher percentage replacement, did better as far as their ability to stop smoking.

Q. Another article that was published in JAMA was the "Mortality Following Inpatient Addictions Treatment: Role Of Tobacco Use in a Community-Based Cohort." First of all, what's a community based cohort, doctor?

A. Well in Rochester we have the ability to kind of follow people over time through our medical index system, and so that -- that makes it a population-based cohort. "Cohort" is just a collection of -- of people in -- either a certain

group of people or a certain geographical area. This was a retrospective study where we looked backwards in time, identified people who had been through our addictions treatment program, and then followed them forward in time to see what their outcome was, what happened to them. And the main -- the main thing we did as far as the main outcome we measured was whether or not they lived or died. Mortality.

So mortality is, in outcome language, it's probably the ultimate outcome. And so by measuring that we can measure it through death certificates and have a very finite end point.

So these people had been in treatment for their alcoholism, and it dated back to the early 1970s and went forward to the early 1980s, and we followed them through our index system until the early 1990s. And what we found was that the people who had been in treatment for their alcoholism and other drug dependencies died at a higher rate than you would expect for the general population. A much higher rate.

The second thing we found, when we looked at the causes of death in those people who died using a standard classification system from the Center for Disease Control in Atlanta and relating those to

alcohol-related diseases or tobacco-related diseases, over half -- over half of the people died of tobacco-related diseases like lung cancer, heart disease, emphysema, and only about a third died of alcohol-related diseases. And the message of that study was that if you're going to be treating people with this kind of problem, then you need to pay attention to their nicotine dependence because it's responsible for over half of the mortality that will occur in the future. And if you're not going to treat that, then that's really not good practice. And that's really had an effect on the -- the community of -- treatment community for people with other addictive disorders because -- because it has the message of mortality rather than other outcomes.

Q. So that these -- the cohort here and the people you were looking at were those who had alcoholism?

A. And other -- and other addictions. It may have been alcoholism plus other -- other dependencies. Had about 75 or so percent or 80 percent were also nicotine-dependent. But we took all the outcomes, we didn't slice it any way. Every outcome was taken at the end. Even though they may have been a non-smoker -- there were a small number that were non-smokers in the cohort, so that's still included

in the bottom number, the denominator of the equation, and the top part of the equation is the people who died over the 800 or so people who were -- who we followed over time.

Q. Doctor, another article is entitled "Nicotine Dependence Versus Smoking Prevalence: Comparisons Among Countries and Categories Of Smokers," which was published in 1996 in Tobacco Control. Can you describe briefly that article?

A. Well this was a cooperative effort from other people in other countries. After you've been doing this for a while you get to know people from other places, and the person that was the lead author on this was Dr. Fagerstrom, who's a scientist from Sweden, and he was interested in knowing what the ratings of nicotine dependence were in -- from one country to the other, and he developed many years ago a questionnaire that is used throughout the nicotine dependence treatment community that defines, as best we can, degree of dependence. It's called the Fagerstrom Tolerance Questionnaire.

So he was interested in knowing what might be differences from different countries of the score on this particular test, which gives a gauge of how dependent a population might be. And so that's

really the thrust of that study, to see what the dependence level was of different populations.

Q. And what was found in that study?

A. It varied, and it varied according to the studies. People who may come to a clinical treatment program like ours that we would run for a nicotine patch study might have higher levels on the Fagerstrom Tolerance Questionnaire than people who were just asked the questionnaire as part of another medical encounter. So people seeking treatment might have higher levels of dependence.

Q. The questionnaire you mentioned, what was that called in?

A. The Fagerstrom Tolerance Questionnaire.

Q. Can you describe what that is for the ladies and gentlemen of the jury?

A. Well it's -- it's a series of questions that has to do with smoking behavior. One of them has to do with how long after you get up in the morning do you have your first cigarette? It also has how many cigarettes a day that you smoke. Do you smoke in places that it's normally forbidden to smoke, like theater is and churches? And all those things have to do with what we term the level of dependence. A person who would smoke in this courtroom I would

suspect would have a very high level of dependence,

otherwise they wouldn't -- wouldn't be doing it. So those are the kind of questions that are there.

And a person who gets up in the morning, like I used to, before my feet hit the floor I would have my first cigarette going. So that person would fall into the category of having a higher level of dependence because I would be smoking the cigarette earlier than someone who could wait until 30 or 40 minutes or an hour or two after they got up in the morning.

It's just a gauge or a measure on how dependent a person might be. And it's not -- it is the best tool we have right now, but it's not perfect.

Q. Doctor, there's one other article that was published in Pediatrics in 1996 which was entitled "Nicotine Patch Therapy in Adolescent Smokers." Can you describe what the nature of that study was?

A. In all the work that's been done about adolescents, and as you all probably know, if you don't start smoking by the time you're 21, the likelihood of you being a smoker later on is very small. Actually, if you don't start smoking before the age of 18, the -- the chances of you becoming an adult smoker are very small.

And there's been a lot of effort expended in the public health community to try to help understand how to prevent kids from starting to smoke. There's been a lot of effort in that regard. But there have been very few efforts to try to treat teen-age smokers, to try to help them to stop smoking. The assumption had always been that kids aren't particularly interested in stopping smoking, and that was a bad assumption. And so when you looked at the literature, when we looked at the literature to find out, well, what is there out there about treating adolescent smokers, and by this I mean age 18 -- under age 18, there really wasn't very much available. So we did this as a pilot study to see, one, if any -- any teen-ager would come to be treated for their nicotine dependence, and two, what the safety of the use of this product would be in children. We know what it was -- we know it was safe to use in adults, but we'd never used it in children. No one had ever used it in children. And then the third was to see if we could help them stop smoking.

So the answer was we -- we had kids who wanted to stop smoking. When we --

One of the things you have to do when you do adolescent study, you have to have parent consent,

which is a little bit of a barrier, because when we put the notices out in the schools and in the newspaper, we had a -- had a program for adolescent smokers, we got a lot of telephone calls, and they were very interested until we said well you need to come to this information meeting and, oh, by the way,

you have to bring your mom, dad, or your guardian to sign for you. So the numbers went down a lot with that. Nonetheless, we had 22 kids who signed up for this program.

The patch was safe, it didn't cause any adverse events. And unfortunately, only one of the 22 was able to maintain her abstinence over the entire year after being treated in a standard course of therapy. A large percentage of them reduced their smoking, but only one was able to stop smoking.

When we did this questionnaire, the Fagerstrom questionnaire, the results of that were basically the same as you would see in adult smokers. These kids were as addicted as their adult counterparts.

Q. Now have you made, in your field of specialty, presentations at various national meetings?

A. I have.

Q. Okay. You've spoken at the Seventh World Conference on Tobacco and Health in Perth, Australia,

in 1990?

A. Correct.

Q. You spoke at the Eighth World Conference on Tobacco and Health in Argentina in 1992?

A. Yes.

Q. And the Ninth World Conference in 1995 in Paris, France?

A. Correct.

Q. And you've also been invited to speak at various educational institutions around the country and the world?

A. Correct.

Q. You've spoken at Johns Hopkins Symposium on New Developments in Nicotine Delivery Systems?

A. Correct.

Q. At the University of Texas, the Southwest Conference on Nicotine Dependence?

A. Yes.

Q. At the University of South Dakota for Nicotine Dependency Treatment Program at the Internal Medicine Grand Rounds?

A. Right.

Q. At Indiana University, Smoking Cessation Treatment: Trends in Smoking and the Benefits Of Quitting?

A. Correct.

Q. At St. Louis University -- excuse me, Washington University in St. Louis, Missouri, Smoking Cessation in the Primary Care Practice?

A. Correct.

Q. At the University of Tennessee, Update on Addiction Treatment?

A. Correct.

Q. Louisiana State University, Conference on Smoking Cessation in Nicotine?

A. Uh-huh.

Q. At the Henry Ford Hospital in Detroit, Michigan, Indicated Nicotine Dependence Therapy?
A. Correct.
I might add at that particular institution, they have adopted the model that we started at our place and have now a nicotine dependence treatment program similar to but not -- not to the extent that we have.
Q. How many programs are there like that in the country, doctor?
A. Like our program?
Q. Yes.
A. I don't know of any other one that's like this, that integrates practice, education, research, one, and two, that has the levels of intervention, because

we have individual treatment, group treatment and inpatient treatment for the patients. So that's really the only one that I'm aware of that's like that.
Q. You've also spoken at the Wayne State University, Michigan Cancer Foundation in Detroit, Michigan?
A. Right.
Q. And at the University of Nebraska Medical Center, The Use of TransDermal Nicotine for Cigarette Smoking Cessation?
A. Correct.
Q. "Transdermal," those are patches?
A. That's correct, yes.
Q. You've also given testimony in front of the FDA Drug Abuse Advisory Committee?
A. That's correct.
Q. And you've spoken at the University of Wisconsin, LaCrosse, on going smoke-free?
A. Yes.
Q. Free workshop for businesses and restaurants?
A. Yes.
Q. And you've also spoken at the American Psycological Association in Toronto, Canada.
A. Yes.

Q. And at the Iowa Academy of Family Physicians in Des Moines, Iowa?
A. Yes.
Q. And at the American Society of Clinical Oncology in Denver, Colorado, Clinical Trial Outcomes and the Treatment of Nicotine Dependence in Medical Settings.
A. Yes.
Q. "Oncology" is a word for cancer?
A. Oncology is the treatment of cancer. That's the whole field of cancer treatment.
Q. Now you also are a scientific reviewer for various peer-review journals?
A. I am.
Q. Can you describe what a peer-review journal is?
A. A peer-review journal is -- is like the Journal of the American Medical Association or the Mayo

Clinic Proceedings or the New England Journal of medicine, which receive articles from people who are writing about scientific work, and "peer review" means that -- that the articles then are received by the journal and then sent out to peers. So I might be reviewing articles about smoking cessation or nicotine dependence treatment or nicotine patch therapy for people who might be writing it from another part of the country, they sent their articles

to the journal and they send them out to reviewers who review the articles anonymously, and then send them back to -- it's anonymous to the author, but it goes back to the journal, and then they determine whether or not they're going to publish the article.

So it's -- it's really the highest level, if you will, of journal review process. And it's very difficult. When you have an article that's in the Journal of the American Medical Association, you've gone through a lot of effort to get it there. The science has to be really very good. The writing has to be clear and very good. So it's a -- it's kind of the standard that we look at as far as science within medicine.

Q. Okay. And some of the journals that you have peer reviewed for are Addiction, Alcohol Health and Research World, American Journal Of Epidemiology, Annals of Internal Medicine, Chest, Drug Evaluations, JAMA, which is the Journal for the American Medical Association.

A. Uh-huh.

Q. Journal of General Internal Medicine, Journal of Internal Medicine, Journal of Studies on Alcohol, Mayo clinic Health Letter, Mayo Clinic Proceedings, The New England Journal of Medicine, Patient Care,

section editor for the Mayo Clinic Family Health Book, Tobacco Control International Journal, and the Western Journal of medicine?

A. Yes.

Q. And during the course of your career have you also received various research grants from the National Institute of Health and other companies?

A. From companies and the National Institute of Health. From pharmaceutical -- pharmaceutical companies, yes.

Q. Doctor --

A. I'd like to clarify that the Mayo -- Mayo Clinic Health Book is not really a peer-reviewed journal. It is peer reviewed, but it's a -- it's a family health book that people buy. So it's listed there. But it's not, quote, peer reviewed in that sense.

Q. All right.

A. Carefully written, but not peer reviewed.

Q. Let me direct your attention back to the Nicotine Dependence Center at the Mayo Clinic, and I'd like to go to the origins of it so that the court

and the ladies and gentlemen of the jury have an understanding how that Nicotine Dependence Center came into being.

It was first called the Mayo Smoking Clinic?

A. Let me just get a drink.

Well the origins of the Nicotine Dependence Center actually came from The Smokers Clinic that we talked about earlier. And as I said earlier, in 1975 there was very little that was available for patients. We could do heart transplants, kidney transplants and other things, but we only had this one community-based program for patients who were trying to stop smoking.

So I actually went to that program. My wife called me at work one day and said, you know, we need to do something about our smoking. I've signed us up to go to The Smokers Clinic. And The Smokers Clinic was the only thing that we had available. So we went.

I was able, fortunately, to stop smoking as a part of that. It was before patches and gum and things like that. It was the hardest thing I ever did. And as a result of that, I then went back as a group facilitator, because I had had training in my -- in my internal medicine program where I went through the addictions unit and had training there, and I had skills as -- as a counselor or a person to lead groups. So I came back as a facilitator for their groups after -- the program after I went

through it, and did that for a few years actually.

Dr. Hepper, who was the -- one of the founders of The Smokers Clinic then decided not to be the medical director of it any more, and they asked me if I would do that. This is after I'd joined the staff of the clinic in 1976. I think I became the director in 1977. And I oversaw the work of that Smokers Clinic over the next few years, and as a result of that developed a real keen interest on how to refine that.

At the time we started -- or at the time that I went through the program, there was a little bit of a mention about addiction but not very much. It was mainly behavioral treatment, teaching people how to recognize the cues to smoke, what to do about the trigger situation and how to overcome that, how to overcome the urges to smoke, how to overcome the withdrawal symptoms that might be present, to teach them the behavioral parts of that. So after I became the medical director we began to integrate into that a lot of the things that I knew about addiction medicine which I'd learned from my internal medicine fellowship and my rotation through the psychiatry unit as well as the addictions unit. And we began to really understand that this was something well beyond

behavior. There was a very severe and serious addictive component to it.

Because recognizing the groups of people that we were seeing, that they had the same hallmarks of people that I'd seen earlier in our addictions treatment program: rationalization, denial, loss of control, getting up every morning saying well I'm not going to do this all over again, I'm not going to smoke as much today as I did the day before, but not having the ability to control that. And so we began to integrate into that program the addictions philosophy, if you will.

Now I'll never forget, it was in -- probably in the mid-1980s, I was on hospital rounds. As an internist we make hospital rounds to see patients in the hospital. And received two phone calls in the same day from people that were hospitalized, and at that time we still allowed smoking in the hospital, this was before the smoke-free policy, who had serious limb-threatening vascular disease, they had hardening of the arteries to the point that they had ulcerations on their feet and they were in danger of losing their feet -- or their legs. And desperate phone calls from the vascular service on the one hand and the dermatology service on the other. What do we

have to offer these patients? And we didn't have anything to offer. We had no treatment facilities for them. We could do all kinds of surgery and all kinds of medical procedures and such, but we did not have a treatment program for patients with these life-threatening medical complications of their nicotine dependence.

After that we got a group of people together to try to see if we could develop a set of programs that we might get approved through the institution. We brought that to the institution's attention in 1986 or so, and there was a two-year planning process after we got approval to actually implement the program, which we described earlier. So we started seeing our first patients in April of 1988 and have moved forward to continue to refine and develop more and -- more programs and more effective interventions as we've gone along.

Q. Now you deal with different types of patient groups? By that I mean outpatient or inpatient, or is it all inpatient?

A. No. I want to make sure everybody understands that. Most of the people that we see are referred by a physician from within the complex, and most of those are outpatients. They're coming to be seen for

whatever problem they may have, and maybe -- they just may be there for a health maintenance

examination, just a regular checkup. And I should also tell you that -- that Mayo Rochester, though it has an international reputation, it's really a regional -- a regional facility.

And you have to think about it kind of in concentric circles. In the center circle is Rochester and Olmstead County, and I as a primary-care physician take care of patients from that innermost ring around -- around Rochester. And there are family physicians and there are obstetricians and pediatricians that do the same thing that I do. Then there's another layer around which is kind of a regional practice, and outside that is the rest of the country and the rest of the world.

If you go from the middle part, a very large percentage of our patients come from Olmstead County. If you go to the next level, over half of all the patients seen at Mayo Rochester are from Minnesota. Over 80 percent of the patients who are seen there come from within 500 miles. And only a very small fraction, though they get all the headlines, only a very small fraction come from far away and are the famous people. We really take care of people from

all walks of life.

So those patients that might be referred for treatment that would be seen on an outpatient practice would -- would reflect that. They would be a lot of local patients, a lot of people in Minnesota, Iowa, Wisconsin, and a few from afar.

Then we do see people in the hospital. We provide these same kind of counselor services and intervention services for patients in the hospital. Then the treatment services are kind of in three different tiers: outpatient treatment, group -- group therapy where they come in for special longer sessions, and then the most intensive level of intervention is the inpatient treatment program.

And so you kind of put the numbers together, we've seen the most patients in the outpatient individual one-to-one counselor intervention, and the fewest in the inpatient program. About -- we've had about 250 people in the inpatient program out of the 15,000 or so that we've seen total.

Q. Now are they inpatient just for nicotine addiction, or is it inpatient for other reasons also?

A. It is inpatient for nicotine dependence only. We try to address other things, but it's only a week long and things are very complicated, very difficult

patients who are having a hard time with this.

Q. Now earlier in your testimony, doctor, you had mentioned the aspects of treatment, and I think you went through them fairly quickly. They were behavioral treatment, addiction treatment, pharmacological treatment, and then relapse prevention I think you mentioned.

A. Right.
Q. Can you describe each one of those categories or segments of treatment that's undertaken in the Nicotine Dependence Center at the Mayo?
A. Okay. All of the counselors are fully trained in all four of those areas, and if we have a counselor who has had training in addictions, like they may have been in -- three of our first counselors had been counselors in our adolescent addictions unit before they came to work for us. So they had -- they had a real good understanding of addictions treatment, but we had to teach them more about the pharmacologic treatment and behavioral treatment. So if you just kind take them as a list, we need to make sure that all of the counselors are trained in all four of these things.
Behavioral treatment goes back many, many years. The behavioral -- behavioral medicine has been --

they've been treating patients with nicotine dependence for a long time. Behavioral treatment, as we mentioned earlier, would be having the smoker to go through a list and recognize their cues to smoke, recognize the triggers to smoke, recognize the situations that they might put themselves in, helping them to understand and develop skills and helping them develop skills to reduce stress, stress management, help them to develop skills to cope with situations in a different way rather than just smoking. So those are kind of the behavioral skills that we talk about.
Q. Doctor, if I could interrupt you there, you used the term a couple times "triggers" and "cues."
A. Right.
Q. Can you describe what that is? What's a trigger and what's a cue?
A. Well a cue is kind of the word that's used by people in the behavioral field. Trigger, if you -- for me, after I'd stopped smoking even just for a little bit, there would be a situation that would occur like a cup of coffee, or talking on the telephone, driving the car. I didn't really realize until much later that the car actually would start without me lighting up a cigarette, because the

ritual was get in the car, put the key in the ignition, put the lighter on, get the cigarette out, by that time the lighter had popped out, put the cigarette in your mouth, light the cigarette, and then start the car. So that was -- so I had to recognize I need to unhook from that behavior. So that was a cue. That was a trigger.
Q. So it triggers a memory of smoking; is that --
A. It cues --
Actually if you get down to the pharmacology of it, it triggers the response that happens in the brain to very high levels of nicotine that get into

the system when you smoke a cigarette, because a cigarette is the most efficient delivery form of nicotine that exists. It's better than intravenous. The levels you receive in the brain are very high, and the outcome of that is the sensation that you receive there is part of the cue response, it's part of the trigger response. And even people who have stopped smoking for a long time, maybe even a year or so, will have certain situations that will trigger that memory, if you will, of what it was like to have those levels of nicotine in their brain. And so they -- they remember.

It's like if someone would light up a cigarette

across the room and it was a fresh cigarette, had that smell to it that was a fresh cigarette as opposed to stale-smelling cigarette, that might ignite this cue response. A glass of wine, a cup of coffee, a fight with a spouse. I mean there are all kinds of responses that would -- where a cue response or a trigger that might occur.

So we need to teach the patients what do you do? What do you do the next time you have that stress or that situation, how do you avoid that urge to go ahead and have a cigarette. And people had to remember that the urge to smoke, those cravngs, though they may be very intense, they're very short. That's one of the things we try to teach them.

But the teaching has limitations, and that's where the addictions part of this comes in. Behavioral treatment or teaching a person about their own behavior and what they're going to do about it is only part of the equation. It has limitations. And by that I mean the -- the patients have to really understand that -- that we're dealing with an addictive process, an addictive disorder. So though we can teach about all these things, sometimes the overwhelming urge is the drug driving the equation. The drug is taking control and the person with the

problem has no control over that.

And there's a tendency on the part of most smokers that we see who have -- have nicotine dependence, to use the same things that other -- other people with other drug addictions would: rationalization, denial, not recognizing that they've lost control. And so those are the things that have to do with addictions treatment that both the counselors and physicians need to understand. Because the tendency is to blame the smoker, and -- and the smoker isn't the problem, the drug is the problem. The drug has exercised an element of control over the individual and their behavior.

Q. Now you say the counselors have to --

THE COURT: Counselor, counsel, why don't we take a short recess.

MR. CIRESI: All right.

THE CLERK: Court stands in recess.
(Recess taken.)
THE CLERK: All rise. Court is again in session.
Please be seated.
BY MR. CIRESI:
Q. Doctor, I'm going to ask you to repeat your name real loudly. Some of the jurors did not hear your

name when we first started this morning.
A. Okay. My name is Richard Hurt, H-u-r-t. Like a pain, so to speak.
Q. Doctor, when we recessed, we were talking about the four categories of treatment at the Nicotine Dependence Center and we were on that category entitled addiction treatment. And one of the points you had made is that the counselors must understand the issues that the individual smoker is dealing with, and can you describe what you mean by that?
A. Well it -- it actually goes back to one of the training encounters, and actually when we have our training seminar to train people from other institutions who want to learn how we do what we do, that's one of the key points, because we've always heard about the behavior of smoking but we need to learn and understand the addictions part of -- of smoking and nicotine addiction and how that works. And so what I think I was getting ready to explain was those things have to do with denial, rationalization.
Denial is like I might have a -- a pulmonary problem, a lung problem, emphysema for example, or even chronic bronchitis, and to be able to mentally detach from that and deny the connection between my

smoking and that lung condition, it would be like a person with alcoholism who has cirrhosis but is able to deny and rationalize that those two things aren't connected. That is the addiction part of this. That is the drug speaking as opposed to the individual.
And so the tendency, as I said, I think, earlier, is to blame the smoker for this, and really it isn't the smoker at all, it is the drug itself that is in control of those situations. And so the denial and rationalization that occur have to do with loss of control.
Q. Okay. And what type of treatment is rendered in this phase in the addiction treatment? What is done?
A. Well it's mainly counseling, because it's important for the patient to understand this so that you don't feel guilty about this. I mean there's enough guilt amongst people who are smokers already, and so if they understand that it is a loss of control and that we're dealing with nicotine as a drug of dependence or a drug of addiction, then it's helping them to step back a little bit and understand -- understand that and to -- to know that

we're talking about a biochemical phenomenon, not just something having to do with I'm -- I'm a bad person, because that's just not the case. And

smokers are ordinary people who happen to be dependent upon the drug and the drug is called nicotine, and when it's delivered by the most efficient delivery device available, the cigarette, it produces high levels of addiction.

Q. Now the other -- the third category of treatment you mentioned was pharmacological treatment. First, can you describe what "pharmacological" means?

A. Well pharmacology is the study of drugs and the way drugs work in the body. And this is kind of the newest area that we have available. As I think I mentioned yesterday, nicotine patches have been around for -- well, for seven years now. Nicotine gum has been around for maybe ten years. And those -- nicotine gum was the first pharmacologic treatment that we had available to help people stop smoking. The patches came out. There is a nicotine nasal spray, another delivery device for nicotine. There will be a nicotine inhaler next year, which is a little puffer that people with puff on to get nicotine inside their mouth. So those are kind of the nicotine-delivery devices that -- that we have to treat patients.

And then probably the most exciting thing that's happened more recently is that we have a non-nicotine

drug to help stop smoking, it's called bupropion, the trade name for it is Zyban, and we published an article in the New England Journal of Medicine just last year to do with that drug. It's a very helpful treatment, it's not a cure-all.

So those are kind of the things we talk about when we talk about pharmacologic therapy. So it's -- it's an expanding area. We're now using those drugs in combination, patches plus bupropion, nasal spray plus patches. We're trying to figure out different combinations to help people stop smoking better. And kind of the -- we're at the very early phase of the understanding of the biochemistry of all this and the biochemical reactions that occur in the brain.

This last drug I mentioned has to do with dopamine. Dopamine is a transmitter in the brain that has to do with pleasure and reward when it's released in certain areas of the brain, and those areas are activated by drugs of dependence like cocaine, opiates and nicotine. And so this drug has to do with dopamine. It actually increases the level of dopamine in the brain and helps people stop smoking through that mechanism.

So we've learned a lot in the last ten years on how best to treat patients using pharmacologic

therapy, but we've got a long way to go. We're kind of where we were, you know, 50 years ago when we only had penicillin and sulfa drugs to treat infections. We're kind of at the beginning of this. And in the next ten years I suspect we're going to learn a lot more.

Q. Now the last stage or category of treatment was what you designated relapse prevention. Can you describe what that is, first of all, and then secondly what it entails?

A. Well as you probably know, people who are smokers, who stop smoking for a little while, tend to relapse. For example, people who see one of our counselors in our program and receive all that they can give in an individual counseling session and have the follow-up visits and so on with the counselors, only about 22 percent of those people will stop smoking and remain abstinent at the end of one year. And some may start out by -- by being abstinent or having stopped smoking for a few weeks, but then relapse. They come under a stressful situation or they have some cue to smoke or they let their guard down and think they can just have one, which isn't really possible for most of us. And so we need to figure out how better to help them in those

situations to avoid relapsing. So that whole area has to do with preventing relapse.

So we teach them a lot about it, talk to them a lot about it, and then we call them up on the telephone at specified intervals, one month, three months and six months, and try to maintain contact with the patients to help them through those situations. We send them a series of letters. So we try as best we can to maintain contact with the patients in order to help them not to relapse, and if they do relapse, to let them understand that there is more treatment that we can provide for them.

Q. Now you said that only 22 percent at the end of a year, one year, are not smoking.

A. Right.

Q. Is that dependent upon whether they were had inpatient, outpatient, or is that across the board?

A. That's kind of across the board. For people who receive the individual treatment or the individual -- and it's really very brief, it's one consult with -- the counselor spends 45 minutes or an hour with the patient, and that may be the only time that they have to spend with them. They may have a follow-up visit, but it may be just the one. So it's really --

If you look at the overall statistics of people that stop smoking and the whole -- whole realm of smokers from one year's period of time, probably less

than five percent of smokers who try to stop are able to stop smoking on their own. If they see a physician, we can double that rate to around 10 or 11 percent. If the physician has some intervention they provide to the patient, and with our counselor intervention, we can provide upwards of 22 or so percent, so it's a four times as good as trying to stop on your own. And then if we go to the higher levels of intervention, like the inpatient treatment program, 43 percent of those are able to stop and maintain their abstinence for a year. Which on the surface sounds really good, but at the same time there's a large number that relapse too. The majority actually relapse.

So this is an area where we know the least about this as far as how to do it and provide relapse prevention for -- for the patients.

Q. How much of your career, doctor, at the Mayo is spent on nicotine addiction and the treatment of it?

A. About half the time right now. It varies. It's hard to gauge that because the work week is long, and in the 50-hours-or-so work week, it would be about

half the time, maybe 60 percent of the time is spent only in nicotine addiction treatment and helping the counselors, helping the patients.

Q. Now in 1995 were you asked to consult with the state of Minnesota and Blue Cross and Blue Shield in this case?

A. I think that's right, yes.

Q. Have you ever testified before?

A. No.

Q. Did you have to get approval from the Mayo Board of Governors in order to testify?

A. I did. And this is a little bit of an unusual situation. I asked for permission and had -- that had to be approved at the highest levels of our institution, which is the Board of Governors which oversees Mayo Clinic Rochester, but also had to be approved of the Board of Trustees, which is kind of the next level up, and they approved my participation in this case.

Q. Now you've conducted an investigation in order to prepare yourself to testify here on the issues that you're going to be facing?

A. I did.

Q. Did you look at internal documents from the industry?

A. I did.

Q. Did you request documents from our law firm that we obtained from the defendants so that you could review them?

A. Correct. My area of interest and expertise has to do with what we've been talking about, which has to do with addiction or dependence, has to do with what happens in people who smoke and how they might

compensate if there is a lower delivery systems that might be available. Those are two of the areas I requested information on, how nicotine may have been changed or manipulated as far as the form is concerned and how that might affect the addictive potential of the drug or -- or the areas that -- that I had interest in.

Q. And doctor, before you looked at those documents, had you kept abreast of the literature in nicotine addiction and dependence?

A. Correct. It's -- it's --

When you get to kind of this stage, it's not hard to because you end up reviewing articles that are sent, you get phone calls from colleagues around the country, so it's kind of a continuous education process almost on a daily basis.

Q. That would be a normal state of affairs for

doctors. You keeping abreast of information as you go along?

A. Well as best you can. But when you kind of get into a special area like this, there -- you may get a phone call from someone wanting to know what this blood level means. And that happens probably every -- every other day or several times a week. A patient is being seen, say, at Indiana University that's on the transplant list for a heart transplant, and one of the -- one of the issues with heart transplants and lung transplants is whether or not the person is continuing to smoke. Which people say, well, that's -- why would anybody continue to smoke if they're trying to get on a transplant list? Well, it really has to do with the degree of dependence or addiction that the person has.

We've got lots of patients who continue to smoke even though they have a severe tobacco-related disease who may be on a transplant list or trying to get on a transplant list. So --

Just last week I got a phone call from Indiana University. They wanted to know how to interpret a cotinine level in a patient that they were proposing to put on the transplant list. So I get -- those sort of calls come in. And just as a result of those

things you kind of have to keep up. So that's a little bit different than -- than my internal medicine practice where I have to -- have to go to the journals and the textbooks and so on and kind of keep up on our own. These things make me keep up because I get inquiries from around the country.

Q. Did the documents of the defendants that you reviewed expand your knowledge base with regard to nicotine and its addictive capabilities?

A. In ways that -- that are just hard to describe. I -- there are some areas that we'll probably get into that -- that I had not even dreamed that there was this much work that had been done over the years.

Specifically with regard to pH and nicotine manipulation, those were things that were basically not known to the level that -- that they're known in the internal documents.
Q. And you've prepared an expert report in this case?
A. I did.
Q. Did anybody tell you how to testify or how to limit your opinions in any way?
A. No.
Q. Now you've been asked to give your expert professional opinion on the following subjects,

doctor: whether nicotine is an addictive drug; correct?
A. That's correct.
Q. Whether the defendants knew they were selling an addictive drug.
A. Correct.
Q. Whether nicotine in free base form maximizes its potential to addict smokers.
A. Correct.
Q. And whether the defendants intentionally misrepresented the health risks of smoking by marketing low tar/low nicotine cigarettes as health reassurance products.
A. Correct.
Q. And also whether the defendants intentionally misrepresented the health risks of smoking by creating doubts about the health risks.
A. Correct.
Q. And finally, whether the defendants' actions were a substantial contributing cause to people smoking.
A. Correct.
Q. Okay. Are you prepared to express your opinions on those subjects here during the course of your testimony?

A. I am.
Q. Okay. I'd like to review with you, doctor, the type of information that you have examined that forms the basis of the opinions that you're going to render here over the course of the day and probably tomorrow.
First of all, in your training and in order to prepare yourself for dealing with the Nicotine Dependence Center at Mayo, have you familiarized yourself with the history of smoking?
A. I have.
Q. And do you at the clinic in the Nicotine Dependence Center utilize an historical perspective of the use of tobacco for the purpose of treating patients?
A. It's important for them to understand. Yes.
Q. Can you turn in -- I believe it's book number one in front of you -- actually it would be book

number two. I'm sorry.
A. Okay.
Q. -- to Exhibit 30083, and I'd like you to describe briefly as we go through these exhibits, which are for illustrative purposes only, the history of tobacco in this country.
A. Well the way that -- that I explain this to our

staff and to our patients --
MR. BERNICK: Your Honor, I object to this line of questioning. I don't think there's a foundation for it. I'm prepared to conduct some voir dire.
THE COURT: Overruled. You may answer.
A. In understanding the issue of the current use of tobacco, it's important for all of us, and especially for the patients and for the field, to understand where we've been for the last several hundred years. There is this thought out there that cigarettes have been around since the beginning of time, that they're somehow mentioned in the Constitution or the Declaration of Independence, but cigarettes did not exist in those days. Cigarettes are a modern phenomenon, and though they existed in the latter part of the 19th century, they really are a 20th century phenomenon that has occurred. So it's helpful sometimes to kind of go through some of the history of this, and -- and that's what's outlined on -- on the overhead.
Everyone knows that tobacco has been around for a long time, that people have used tobacco since antiquity. And it's actually a Western Hemisphere phenomenon. The natives of North Central and South

America use tobacco for a lot of different reasons; they used it ceremonially, they used it in an addictive way. There's a group of Huron Indians in the northern part of the country that -- who have been found to have used very large quantities of tobacco smoked in pipes, and it's theorized that they had very large usage. So this is something that was present when the early European explorers came to the United -- to the -- to the New World and they discovered that the natives were using tobacco. And they took it back with them. They -- they were amused by this, some were, and others began to use it themselves.
And the third point, the Portugese explorers really are credited in some way for basically making this circle the globe within the period of a hundred years, which is very, very unusual for a product to be able to do that in such a short period of time in those -- from that -- in that century. They would take the seeds of tobacco from -- from one port or from the New World and take them with them and leave seeds. And then it basically circled the world. So tobacco use was something that -- that the European

explorers found when they came here. They took it back with them, back to Europe as well as around the world.

The last person on the list here is Sir Walter Raleigh, who popularized pipe smoking back in the 17th century. And there's an etching that I could -- can recall of his servant getting ready to throw a pot of water on him because he was smoking his pipe; the servant thought he was on fire because it was an unusual thing to see someone smoking -- smoking tobacco.

The next one is kind of a continuation of this because as -- as tobacco began to be grown, it became a very important product. And the American colonies began to grow and export it. The colonies which were involved are the ones listed here, but tobacco can be grown in almost anyplace. Wisconsin used to be a very large tobacco-growing state. Still is. Tobacco can be grown in Canada, tobacco can be grown in a lot of different states. Though it was focused in the Carolinas, Virginia and the South, it can be grown in a lot of different places.

It was a major export product for us to Britain. And as I've mentioned here, a hundred million pounds in 19 -- in 1775 was a very large amount of tobacco. And that almost became a currency for the early colonies. The forms of tobacco, though, were pipes,

snuff and chewing tobacco, not cigarettes. Cigarettes didn't really come around until much, much later.

The next one kind of shows the predominant form of tobacco use around the world at that time, which has to do with cigars in Spain, snuff and chewing tobacco in England, snuff in China.

THE COURT: Excuse me, doctor. Doctor, excuse me. Yes.

MR. BERNICK: Yes. I believe that the witness is now referring to an additional exhibit, 30084, I guess, and I don't know what Your Honor's preferred procedure is, but I don't believe the foundation has been laid for this exhibit with this witness, and I believe that this area exceeds the scope of the expertise that's been established with prior questioning, so I would object to the use of the exhibit and further request that counsel not display an exhibit until the court has determined it can be displayed to the jury.

MR. CIRESI: These are part of the same series of exhibits, Your Honor. They were individually numbered only to have an individual number on them, which we will identify at the end of his comment on this particular portion of this series

of exhibits. And they're for illustrative purposes.
THE COURT: You may proceed.
MR. BERNICK: Just for clarification, Your Honor, is there -- I'm sorry, is there --
THE COURT: Counsel, your objection is overruled. You may proceed.
MR. BERNICK: Okay.
BY MR. CIRESI:
Q. Please proceed, doctor. You were talking about the types of -- or forms of tobacco that were used in different countries, which is on the next in this series of exhibits.
A. Correct.
Q. And it's 30084, for illustrative purposes only.
A. The types of tobacco that were used around the world became almost unique to some countries. Most of us have a recollection of some of the early Dutch portraits which would have a long-stem pipe, a small clay pipe that was used. So pipes were used there. Snuff in Scandinavia. And these are other forms of tobacco use in these countries at that time, 18th and 19th centuries.
Conspicuously absent from this are cigarettes because cigarettes didn't come until much later.
Q. Can you move to the next exhibit, doctor, for

illustrative purposes. It's Exhibit 30085, which talks about the origin of cigarettes. And if you could briefly describe what's depicted on that exhibit.
A. There were several things that occurred in -- in the course of history that really made it possible to change the delivery system, if you will, from pipes and chewing tobacco and snuff and cigars, and one was a curing process that's mentioned here that was discovered accidentally. And there are various stories about how that was discovered, but basically there was a -- a heating -- heating of the tobacco that was hanging in a barn because some sawdust caught fire, and the heat rose through the barn making a -- a different leaf, it became called bright leaf, and it had a more acidic -- it was more acidic, had a higher carbohydrate content, and therefore was easier to inhale.
As you have higher pH in a tobacco product, it makes it harder to inhale it because when you get to a pH of eight or so, like in cigars or in pipe smoke, it's harder to inhale because it's harsh. So that was a process that was basically discovered -- discovered by accident.
And cigarettes began to be produced probably

around the time of the Civil War, shortly thereafter, and -- but they were hand-rolled, and the main -- main tobacco that was used was called turkish tobacco, and they became a luxury item for people in

the cultural centers of this country as well as in Europe, like in London and Paris, as well as New York and Philadelphia. Being hand-rolled, they were very expensive. And the factories that produced them were limited; there were only a few of those. And a good hand-roller, a person who could roll these things, could only roll a certain number in a day, around 2,000 cigarettes a day, so the product was expensive and it was really only used by people who could afford it.

Q. Could you move then to Exhibit 30085, continuing with regard to the origins of --

A. This is the second page of the same exhibit.

Q. Second page.

A. Yeah.

Q. Correct.

A. In the 1870s, as cigarettes became to be more popular, there were more cigarette factories or more cigarette companies, and there was a company called Alan and Ginter who wanted to have a mechanical rolling machine to be developed, and they offered a

product and a man by the name of James Bonsack won the contest. And he had invented a machine that could produce and roll 120,000 cigarettes per day, which greatly increased the capacity or the potential capacity of factories to produce cigarettes. He actually offered this for sale, or the rights to it, back to Allan and Ginter, and they declined to buy the rights to the machine by saying, "Gee, we don't know what we'd do with all those cigarettes that would be produced. There's not a market for them. They would produce too many cigarettes for us to even be able to sell them all."

James Buchanan Duke, on the other hand, was a man who I'll talk a little bit more about in a moment, who -- his father, Washington Duke, had formed a tobacco company when he returned from the Civil War, and his son, James Buchanan Duke, who became basically the president and the driving force behind this company, recognized that the Bonsack machine and cigarettes were the future for the tobacco industry. He made a special arrangement with Bonsack to have the rights to this machine, and the arrangement went like this: He would be able to buy the machines always at a cheaper price than his competitors, so he was always able to -- to have the

machines available to him cheaper than his competitors could.

Q. Could we go to Exhibit 30089, which is a -- I'm not sure how good that will come out.

Is that a drawing of the Bonsack cigarette machine?

A. That's correct. That's a -- that's from a patent of the machine that was patented by Bonsack. Pretty crude-looking device, but obviously worked.

Q. And the number off to the left there, 238,640, that would be the patent number in the United States Patent and Trademark Office; is that correct?
A. As far as I know, yes.
Q. Okay. We move on then to Exhibit 30087, the next slide in this overview of the tobacco industry.
A. And this has to do with kind of where I left off with Washington Duke, who returned from the Civil War, and one of the few things that was left on his farm that -- at the time in North Carolina was last year's tobacco crop. He decided to sell that as a way of getting started again after the war was over, and he and his son, as well as his other sons, then developed this company called Washington Duke & Sons, and they began to produce tobacco products, and one of the tobacco products was cigarettes.

So you can see in 1881 they produced 10 million cigarettes. The Bonsack machines were installed in 1884, and within a couple of years they were producing hundreds of millions of cigarettes. And as a result of that the price went down and became available to ordinary people rather than just available to the people who had more money that could afford them.
Q. Can you now direct your attention, doctor, to the next slide, which is 30088.
A. Under the leadership of James Buchanan Duke, he took the Duke Company to heights that no one ever dreamed would be possible. He took his lessons from other monopoly builders of the day, Rockefeller was one, but going into a area, producing this -- or marketing the cigarettes, lowering the price of those, driving the competition out and then buying the competition. And he did that very successfully. And in 1889 he had four of the companies drawn together with the Duke Company to form The American Tobacco Company, and that was the real first major tobacco company in this country, and it was led by James Buchanan Duke at the tender age of 32.
In 19 -- in 1898 he acquired the R. J. Reynolds Tobacco Company, and R. J. Reynolds was a company

that mainly produced chewing tobacco. R. J. Reynolds had come back, in a similar sort of situation, to -- to North Carolina after the Civil War and began producing chewing tobacco and began using burley tobacco in -- in that process. And you can -- it's understood that burley tobacco and the cellular size of it and the fact that you could add flavorings and things to burley tobacco would make the chewing tobacco more attractive.
Duke continued on with his building of his monopoly, and by 10 years later, after the formation of The American Tobacco Company, they basically had a monopoly on all tobacco products in this country. Over 90 percent of the cigarettes, over 80 percent of

the snuff, over 60 percent of the plug tobacco and over -- almost 60 percent of the smoking tobacco, smoking tobacco like pipe tobacco. So they basically had a monopoly on the products in this country.

And he began to do the same thing in England that he had been able to do here, and that is to go into a market, lower the price, and begin to take over companies. And in that time the tobacco companies in England decided to ban together to form a new company called the Imperial Tobacco Company, which became the main tobacco company in England to

confront Duke, and they would put up a stronger united front. And they made a deal between the two companies, between Imperial Tobacco Company and The American Tobacco Company, to basically divide up the market in the world. And it went like this: The American Tobacco Company would have rights to the United States, Imperial Tobacco Company would have the rights to the United Kingdom, and the new company called the British-American Tobacco Company would have the rights to the rest of the world. And so they basically divided up the world and moved forward.

Q. And can you go to the next slide of Exhibit 30088. What happened then in 1911?

A. Well there was a suit brought, and I think that was brought in 1907, that had to do with a -- an antitrust action against The American Tobacco Company because of this monopoly. It had attained a monopoly of tobacco products in this country, and they also acquired other companies like R. J. Reynolds along the way. And the United States Supreme Court dissolved the Duke Trust in 1911, and out of that Duke -- out of that dissolution of the Duke trust came The American Tobacco Company, R. J. Reynolds, Liggett & Myers, and P. Lorillard. And -- and after

that, then, these companies were able to go on their way outside of the Duke Trust, and R. J. Reynolds Tobacco Company then developed what is considered to be the modern cigarette, the cigarette of this century, and it became known as Camels.

It is a blend -- or was a blend that was different than the other blends that had been available up to that time. Up until that time there was flue-cured tobacco and turkish tobacco blended together, if there was a blend, and what R. J. Reynolds had learned with burley tobacco, through his work with smokeless tobacco or -- or -- or chewing tobacco, was he'd learned a lot about that and he made a new blend, which included all three, flue-cured, turkish, and now burley tobacco, and made it into what's now known as Camels, and that became the new cigarette.

The other two things on this slide have to do with the other companies. Philip Morris was -- was

incorporated in the U.S. in 1919. And then the British-American Tobacco Company purchased Brown & Williamson, a tobacco company in Louisville, Kentucky, in 1927, which then displays the current players.

MR. CIRESI: Your Honor, I'd offer for

illustrative purposes only Exhibits 3083, 3084, 30 -- I'm sorry, I misspoke. 30083, 30084, 30085, 30089, 30087, 30088.

MR. BERNICK: Your Honor, we've lodged a prior objection on grounds of foundations and the scope of this witness's expertise. I don't believe he's been qualified in some of the areas covered. However, they've already been shown to the jury, and therefore I'm not sure what the purpose of this additional proffer is.

THE COURT: They'll be received for illustrative purposes.

MR. CIRESI: Thank you, Your Honor.

BY MR. CIRESI:

Q. Doctor, can you direct your attention in the same volume, volume two, to Exhibits 19003 and 19004. And were those examples of the types of ads that were utilized by RJR when they launched the Camel cigarette?

A. They were.

Q. And again, this is part of the historical studying that you've done in order to be able to describe the history of smoking to your patients in treating them at the Mayo Clinic; is that right?

A. Correct.

MR. CIRESI: For illustrative purposes, Your Honor, we'd offer 19003 and 19004.

MR. BERNICK: Your Honor, these, as I understand it, were advertisements that were not listed in the disclosure that was made in connection with this witness's expert reports, both of these, so I believe if that is so, that is what I'm informed, and we would object on those grounds.

Apart from that, I believe that these documents relate to the same objection I had previously, which I believe Your Honor has overruled, and I understand that ruling.

MR. CIRESI: My understanding is they were produced, Your Honor. They were identified, I should say.

THE COURT: Well they'll be received at this time unless -- subject to your being able to show that they were not identified.

MR. BERNICK: Yes, sir.

MR. CIRESI: Thank you.

BY MR. CIRESI:

Q. Describe what we have here, which is Exhibit 19003.

A. Well there were two parts to the Camel story,

one was the new blend, the new cigarette, and the

other was the -- the advertising and marketing, which was the most extensive that had been available up until that time. The -- the first ad has to do with "The Camels are coming," and if you look at this ad you can tell that we're talking about cigarettes, we're talking about the Camels are coming. So this is kind of the entry ad into identifying this as a new product. And there was an extensive campaign throughout the country to -- to get this word out.

Then the next one, which was -- must be 19004 --

Q. 004.

A. -- really has to do with a display that was made to potential store people that might put these types of ads, and so you can see down the left-hand corner, "Camel cigarettes are here." So it kind of went "The camels are coming. The Camels are coming," and now "The Camels are here." So this is a very sophisticated and at that time unheard of national sort of campaign to promote this new cigarette.

Q. And doctor, can you direct your attention to Exhibit 30086, and before it's put up there, is this a chart that you prepared showing early cigarette consumption in the United States?

A. That's correct.

MR. CIRESI: Your Honor, we'd offer this for illustrative purposes, 30086.

MR. BERNICK: I have the same objection, Your Honor, which I note the court has already ruled upon.

THE COURT: It will be received for illustrative purposes.

A. Well this just tells the whole story as far as numbers are concerned, because, as I said earlier, cigarettes really were not a part of our heritage. My great grandparents were not really part of this. My grandparents were because they were born in the 1890s, but my great grandparents really were not part of the cigarettes that we know of the late 19th century and the 20th century. And these are just volumes of production.

You have already seen in 1885, after the Bonsack machines were put on line at the Duke factories in Durham, the rates went up very high. By 1905 there were almost four billion cigarettes consumed in the United States. And then the year of the Camel, in 1913, 1914 and 1915, you can see there was a virtual explosion of cigarette consumption in this country. And it kept on going up until the mid-1960s when several hundred billion cigarettes were consumed in

the United States, whereas before -- as little as, you know, 65 years before that, fewer than four billion cigarettes were consumed in our country.

So this really is a 20th century phenomenon that has the potential to carry on into the 21st and 22nd century.

Q. And doctor, have you also, as part of your study of the addictive nature of nicotine, and in order to treat physicians -- excuse me, patients, have you examined the cancer lung deaths and the prevalence of those and incidence of those over the time of the 19th or 20th century?

A. I have.

Q. Okay. Can you direct your attention to Exhibit 30211 --

A. Okay.

Q. -- and 30212.

Do these two charts show the various cancer rates -- and this is from the Cancer Journal for Clinicians, Exhibit 30211, and 30212 is also from the Cancer Journal for Clinicians -- showing age-adjusted cancer death rates for males?

A. Correct.

MR. CIRESI: Your Honor, we'd offer 30211 and 30212 for illustrative purposes.

MR. BERNICK: I have no objection to those, Your Honor.

THE COURT: Court will receive 30211 and 30212.

BY MR. CIRESI:

Q. If we look first at 30211, doctor, and this is the age-adjusted death rates for females in the United States, 1930 to 1993, can you tell us what is being depicted on this chart?

A. Well I'm going to try to see if I can do this from here, but I think I can.

So this is 1930, and it goes across this way to 1990 over here. This one is breast cancer, the one in the middle. This one is lung cancer. Lung cancer was a very rare form of disease prior to the year 1900. Lung cancer didn't occur very often. Then as you can see, by the mid-'50s and into the '60s and '70s, lung cancer became the most common cause of cancer death in women. It surpassed breast cancer as the leading cause of cancer death in women.

And this number is likely to continue to go up. I've been following this over the last 15 years with the same display, and not too many years ago it was down here below breast cancer. Now that's not the incidence of cancer. Breast cancer is still more

common in women. But as far as a cause of cancer death, it is second to lung cancer as a cause of cancer death.

The next one has to do with men, which is the same display, and as you might imagine the same thing

is true in men. This is lung cancer. It's been the leading cause of cancer death in men since the 1950s, and there's not anything that's even a close second. This represents in this day and time over 30 percent of all cancer deaths in men. Thirty percent.

Prostate cancer is -- let's see where prostate cancer is. Prostate cancer is the dark line, this one. And we hear a lot about prostate cancer, we hear a lot about breast cancer, but lung cancer is the leading death in men and has been for all of my lifetime.

So these two -- these two numbers as far as cancer deaths are concerned account to over 120,000 Americans dying each year of lung cancer, a disease that was rare and practically nonexistent at the turn of the century. And it pales, makes these other ones pale in comparison as far as the frequency of death. This accounts for over a quarter of all of the deaths due to tobacco-related diseases in our country, of which there's over 420,000 Americans each die -- day

dying of tobacco-related disease, so this accounts for over a fourth of those.

To give you an example of how many people 420,000 American's are, that's the equivalent of three fully-loaded 747s crashing every day 365 days a year with no survivors. And this is a quarter of that total number. A disease that was rare at the beginning of the century.

THE COURT: Counsel, I think we'll recess at this time. We'll reconvene at 2:00 o'clock.

THE CLERK: Court stands in recess.

(Recess taken.)

AFTERNOON SESSION.

THE CLERK: All rise. Court is again in session.

(Jury enters courtroom.)

THE CLERK: Please be seated.

MR. CIRESI: Thank you, Your Honor.

BY MR. CIRESI:

Q. Good afternoon, doctor.

A. Good afternoon.

Q. We've been talking about nicotine. What is

nicotine?
A. Nicotine is a substance called an alkaloid. An alkaloid is a nitrogen-containing organic base that's physiologically active. It's like -- other alkaloids are cocaine and opiates as well as nicotine, and quinine is an alkaloid.
Q. Is it toxic?
A. It can be. In fact one of the uses of nicotine is as an insecticide. We have -- I actually have a can of Black Flag nicotine sulfate, which is used to kill insects with. So it can be toxic to animals or -- or to insects or to humans.
Q. Is it pharmacologically active?
A. Yes, it is.
Q. And can you describe what you mean by that?

A. Well "pharmacologically active" means that it has an effect on the -- the person. It can have an effect on the blood pressure or the pulse rate, those would be two of the pharmacologic actions that nicotine can have.
Q. Does it have any effect on the central nervous system?
A. Yes, it does. It's -- a stimulant basically is a -- is a class of drugs and it has that -- that kind of effect. And most smokers notice that, as a stimulant effect, it might be used to kind of keep you awake when -- when you get fatigued. So it has that kind of effect.
Q. Doctor, did you ascertain from the defendants' documents and your review of those documents whether or not the defendants considered nicotine a drug?
A. Yes, they did.
MR. BERNICK: Your Honor, I have an objection to questions that pertain to our documents at this point. I don't believe an adequate foundation has been laid to establish that this witness is an expert in reconstruction of corporate history and corporate knowledge. I have some questions I'd like to ask him in order to lay a further ground work for that objection.

THE COURT: Objection is overruled. You may respond to the question.
MR. BERNICK: Thank you.
A. Repeat the question.
Q. Yes.
A. I forgot it.
Q. Did you ascertain from the defendants' documents whether or not the defendants considered nicotine to be a drug?
A. Yes, I did.
Q. And --
A. And they did.
Q. All right. Can you direct your attention, please, to volume one and to document number 10539. They are in chronological order, doctor.

A. I got it, yup.
February 19, 1969?
Q. Correct.
Doctor, this is a document dated February 19th, 1969, a Philip Morris document from William L. Dunn to Dr. H. Wakeham and is marked confidential. Is this one of the Philip Morris documents that you have reviewed?
A. It is.
MR. CIRESI: Your Honor, we would offer

Exhibit 10539.
MR. BERNICK: Your Honor, we do not have an objection to the document itself, but this document does bring to bear the same objection that I lodged to a previous question, and I have the same objection to this line of examination. I don't want to keep on interrupting the proceedings unnecessarily, and if Your Honor would accommodate this, maybe we can just have a continuing objection to questions that pertain to historical analysis on the grounds that there's not a adequate foundation for it and on the grounds that it's beyond this witness's established expertise, so I don't have to keep reiterating the same objection.
THE COURT: Well counsel, I don't know what all your objections might be in the future, but I have ruled that he has sufficient expertise and it's proper testimony at this time.
MR. BERNICK: Thank you.
BY MR. CIRESI:
Q. This is one of the documents you reviewed; correct?
A. It is.
Q. Okay. Put it up.
MR. CIRESI: We'd offer that exhibit then,

Your Honor.
THE COURT: That exhibit will be received.
BY MR. CIRESI:
Q. Now some of these are older documents, and this one comes from '69, so they're difficult to read. I'm going to direct your attention to the third paragraph, and it reads as follows: "I would be more cautious in using the pharmic-medical model -- do we really want to tout cigarette smoke as a drug? It is, of course, but there are dangerous FDA implications to having such conceptualization go beyond these walls."
Now doctor, this is 1969. Was the FDA regulating cigarettes?
A. No, they were not.
Q. Were they regulating them at the time this lawsuit was filed in 1994?
A. Not to my knowledge.
Q. Is this document of Philip Morris an example of the type of documents that you reviewed of the

defendants with respect to their knowledge that nicotine was a drug?
A. It is representative, and there were literally thousands of pages of documents that I've reviewed over the last year and a half or so, so this is

fairly consistent with the other -- other documents that I've seen.
Q. To your knowledge, has Philip Morris ever publicly stated that they held an opinion as early as 1969 that nicotine was a drug?
A. Not to my knowledge.
MR. BERNICK: Object to the foundation, Your Honor.
THE COURT: I think you need to rephrase that question, counsel.
BY MR. CIRESI:
Q. To your knowledge, has Philip Morris ever admitted publicly, based on your experience, that nicotine was a drug?
A. Not to my knowledge.
MR. BERNICK: Same -- same objection and the same question, Your Honor.
THE COURT: You may answer that.
A. Not to my knowledge.
Q. Doctor, can you direct your attention to Exhibit 18089, which is in volume two.
A. Give me the number again.
Q. 18089.
A. Okay.
Q. This is a document entitled "Motives and

Incentives in Cigarette Smoking," William L. Dunn, Jr., Philip Morris Research Center, Richmond, Virginia, again marked confidential. Is this a document that you reviewed in order to prepare yourself for testimony here?
A. It is.
Q. And is this one of the documents that forms the basis of your opinions that you're rendering in this case?
A. Yes, it is.
Q. And is this document representative of other documents that you reviewed of the defendants in the thousands of pages that you reviewed?
A. It is.
MR. CIRESI: Your Honor, we would offer Exhibit 18089.
MR. BERNICK: No objection, Your Honor.
THE COURT: Court will receive 18089.
BY MR. CIRESI:
Q. First of all, doctor, we see at the top the title, "Motives and Incentives in Cigarette Smoking," and above that to the right is a confidential stamp, and the author is William L. Dunn, Jr., Philip Morris Research Center, Richmond, Virginia.
Do you recall that this document relates to a

conference that was held on an island in the Caribbean waters?
A. That's correct. 1972.
Q. Okay. And can you direct your attention to page three of that document. Again this is document 18089.
If you look at the second paragraph there, there's a reference to who the conference was called by.
A. The Council for Tobacco Research, U.S.A.
Q. And can you direct your attention to the paragraph right below that starting with "Most of the conferees would agree...."
A. Uh-huh.
Q. Do you see that?
"Most of the conferees would agree with this proposition. The primary incentive for cigarette smoking is the immediate salutory effect of inhaled smoke on body function."
And doctor, based on this document, what was being discussed there in in that paragraph?
A. They were talking about the behavior of smoking, and basically we're talking about the cigarette as a nicotine-delivery device.
Q. Okay. Can you direct your attention to page

five of that document, please. I'd like to start at the top with the following paragraph: "Why then is there not a market for nicotine per se, to be eaten, sucked, drunk, injected, inserted or inhaled as a pure aerosol? The answer, and I feel quite strongly about this, is that the cigarette is in fact among the most awe-inspiring examples of the ingenuity of man. Let me explain my conviction.
"The cigarette should be conceived not as a product but as a package. The product is nicotine."
Now doctor, in this document does Mr. Dunn talk about the pharmacologic effect of nicotine on the body?
A. He talks about basically the -- the cigarette as being a dose dispenser for nicotine and the nicotine -- and the cigarettes being a delivery device for nicotine.
Q. To your knowledge, did Philip Morris ever publicly state that at any time up to 1994?
A. Not to my knowledge.
MR. BERNICK: Your Honor, the same objection as before, lack of foundation.
THE COURT: You may answer that.
A. Not to my knowledge.
Q. Do you know if Philip Morris, up through 1994,

ever said think of the cigarette pack as a storage

container for a day's supply of nicotine?
A. Not to my knowledge.
MR. BERNICK: Note my same objection, Your Honor.
THE COURT: Same ruling.
Q. Did Philip Morris ever publicly state think of the cigarette as a dispenser of a dose unit of nicotine?
A. Not to my knowledge.
MR. BERNICK: Same objection, Your Honor.
THE COURT: Same ruling.
Q. Can you turn over to page six. At the top of the page Mr. Dunn states, "Think of a puff of smoke as the vehicle of nicotine." And then next to number two he states, "The smoker has wide latitude in further calibration: puff volume, puff interval, depth and duration of inhalation. We have recorded wide variability in intake among smokers. Among a group of a pack-a-day smokers, some will take in less than the average half-pack smoker, some will take in more than the average two-a-day-pack smoker -- two-pack-a-day smoker." And then finally right below number five, "Smoke is beyond question the most optimized vehicle of nicotine and the cigarette the

most optimized dispenser of smoke."
What is being addressed there in terms of calibration of a smoker with regard to nicotine?
A. Well he's basically talking about the variability between smokers. Some smokers will smoke a cigarette more aggressively than others, take deeper, deeper inhalations, hold their breath longer, so he's talking about the variability. But he's also talking about kind of the threshold that a person has when they smoke a cigarette, having to receive the dose that does the things in the central nervous system, in the brain, to release the neurotransmitters that causes the effects, the pleasure and the reward effects, and those will be different from one person to the next. So this is basically describing how a person might adjust their dose of nicotine by smoking cigarettes, much like a diabetic would adjust their dose of insulin based on how they felt or what their blood sugar might have been.
Q. Doctor, to your knowledge, have any of the defendants ever to this day -- strike that -- ever up until 1994, ever stated that nicotine was a drug and that the cigarette was a dispenser of that drug?
A. Not to my knowledge.

MR. BERNICK: Again, Your Honor, the same objection on which the court has previously ruled.
THE COURT: Okay.
Q. Can you direct your attention now, doctor, to Exhibit 12408, which again is back in volume one of the two volumes in front of you.

Do you have it?
A. Got it. Yup.
Q. This is an RJR confidential document dated April 14th, 1972, written by Claude E. Teague, Jr. Is this one of the documents that you've reviewed for purposes of giving your testimony here?
A. It is.
Q. Is it representative of the documents that you reviewed of the defendants with respect to the issue of nicotine as a drug?
A. Yes, it is.
MR. CIRESI: Your Honor, we would offer Exhibit 12408.
MR. BERNICK: Your Honor, I believe that this is a -- this is a document that was created by Dr. Teague not in the course of his activities at Reynolds but as part of the course that he took at a university, and it obviously, therefore, would reflect the content of what had taken place

at the university which was not an ordinary-course-of-business record. For that reason we would object.
THE COURT: The objection is overruled. The court will receive into evidence 12408.
BY MR. CIRESI:
Q. Now on the cover page it says RJR; correct?
A. That's right.
Q. And it says confidential?
A. Correct.
Q. And along the side there it says "PRODUCED BY RJRTC," which is R. J. Reynolds Tobacco Company. Do you see that?
A. I see it.
Q. And it says it's "PRODUCED IN HUMPHREY," which is this litigation; correct?
A. Yes.
Q. Okay. Now if you go to the very last page, we'll see Mr. Claude E. Teague, Jr.'s signature and the date of April 14th, 1992. Do you see that, sir?
A. 1972.
Q. I'm sorry, 1972. Thank you.
If you direct your attention, doctor, to the first page of text, it says, "In a sense, the tobacco industry may be thought of as being a specialized,

highly ritualized and stylized segment of the pharmaceutical industry. Tobacco products, uniquely, contain and deliver nicotine, a potent drug with a variety of physiological effects. Related alkaloids, and probably other compounds with desired physiological effects, are also present in tobacco and/or its smoke."
Let me just stop there. With regard to that statement, are you aware of whether RJR or any of the defendants ever made such a statement up to 1994, to your knowledge?

A. That they thought of themselves as part of the pharmaceutical industry?
Q. Correct.
A. I'm not aware of any such statement.
MR. BERNICK: Your Honor, it is the same objection. I know Your Honor has ruled, and again I'd be more than happy to -- or I'd appreciate if the court would give us a continuous objection so that I can keep my seat and we can proceed.
THE COURT: Okay. If the question is similar, you'll get the same response from the court. If they start getting different, counsel, you'll have to stand up and object.
MR. BERNICK: I'll be sure to do that.

Thank you, Your Honor.
THE COURT: All right.
BY MR. CIRESI:
Q. Now in your earlier testimony you said that you learned new information about what the defendants knew at given points in time as a result of your review of the documents. Do you recall that testimony?
A. I do, yes.
Q. The last three documents that we've looked at, is that the type of information that you discovered that the defendants knew at various points in time which had not been made public?
A. That's -- to the best of my knowledge, that's correct.
Q. Let me read on in this first paragraph. "Nicotine is known to be a habit forming alkaloid, hence the confirmed user of tobacco products is primarily seeking the physiological satisfaction derived from nicotine -- and perhaps other active compounds. His choice of product and pattern of usage are primarily determined by his individual nicotine dosage requirements and secondarily by a variety of other considerations including flavor, irritancy of the product, social patterns and needs,

physical and manipulative gratifictions, convenience, cost, health considerations and the like."
Now sir, up to and including August of 1994, had any of these defendants ever made any such type statements publicly, to your knowledge?
A. Not to my knowledge.
Q. Direct your attention, then, doctor, to Exhibit 10683. This is again in volume one.
A. Okay.
Q. This is a memorandum by a C. C. Greig, G-r-e-i-g, of BATCo, Ltd. Is this one of the documents that you referred to and reviewed, doctor?
A. It is.
Q. Is this doctor --
Is this document representative of the other documents of the defendants that you reviewed

regarding the subject matter of nicotine and its addictiveness as a drug?
A. That's correct.
MR. CIRESI: Your Honor, we would offer Exhibit 10683.
MR. BERNICK: No objection, Your Honor.
THE COURT: Court will receive Exhibit 10683.
BY MR. CIRESI:

Q. And turn to the first page of the text. I think we'll get a little better -- there.
Direct your attention to the top, doctor. You'll see there it says "STRUCTURED CREATIVITY GROUP, THOUGHTS BY C. C. GREIG -- R&D, SOUTHAMPTON, MARKETING SCENARIO.
"Before starting on any future scenario, let us look at what we are currently selling, where and how it has developed.
"A cigarette as a drug administration for public use has very significant advantages. One, speed. Within 10 seconds of starting to smoke, nicotine is available in the brain. Before this, impact is available giving an instant catch or hit, signifying to the user that the cigarette is active. Flavor, also, is immediately perceivable to add to the sensation.
"Other drugs such as marijuana, amphetamines, and alcohol are slower and may be mood dependent."
Now is this statement by Mr. Greig of B.A.T. Company Ltd. with regard to the cigarette as a drug-administration system something that BATCo, to your knowledge, ever publicly stated at any time prior to August of 1994?
A. Not to my knowledge.

Q. Doctor, I'd like to address your attention now to Exhibit 14145, which has been referred to as the Frank Statement.
A. Okay.
MR. CIRESI: Your Honor, we'd offer that exhibit.
MR. BERNICK: No objection, Your Honor.
THE COURT: Court will receive 14145.
BY MR. CIRESI:
Q. In the left-hand margin, doctor, you'll be able to find the statements that "We accept an interest in people's health...." Do you see that?
A. No, I don't see it. Oh, down at the bottom, yes.
Q. Down at the bottom, right about here.
A. Okay, I got you.
Q. "We accept an interest in people's health as a basic responsibility, paramount to every other consideration in our business.
"We believe the products we make are not injurious to health.

"We always have and always will cooperate closely with those whose task it is to safeguard the public health."

Now with respect to those statements made by the

tobacco industry on January 4th, 1954, what if any significance are those to you, doctor, as a physician?

MR. CORRIGAN: Your Honor, objection. Now the reason for my objection -- excuse me, Your Honor, it's difficult to get up to the podium -- is Mr. Ciresi's reference to "tobacco industry." Signatories to the statement do not constitute the tobacco industry.

THE COURT: Rephrase your question, counsel.

MR. CIRESI: Your Honor, I'm sorry, I didn't hear the last part of it.

THE COURT: You made reference to the tobacco industry, and he indicated that the signatories to the Frank Statement are not all inclusive. You may want to rephrase your question.

MR. CIRESI: Let me rephrase it and take out "tobacco industry" at this point.

BY MR. CIRESI:

Q. With regard to the undersigned statement, who are The American Tobacco Company, Brown & Williamson Tobacco Company, P. Lorillard Company, Philip Morris and Company, Ltd., R. J. Reynolds Tobacco Company, with regard to those defendants who made these

representations to the public, what significance, if any, are those statements to you, doctor?

A. I think it has to do with expectations. I think if an industry were to say that they accept an interest in the people's health as a basic responsibility and use the word "paramount," which to me means the very peak or the very pinnacle or the very top of expectations, to the exclusion of every other consideration in our business, to me that means that the consumer of that product should be assured that the product is safe to use, and that if they were to find out something that was bad about that product they would tell the public, the consumer, the medical community, and everyone else that had to do with these kind of -- of diseases that -- that this product happens to cause.

I think that what they said was that they intended to do that, and I don't think that they did that. They did not live up to their promise.

MR. BERNICK: Your Honor, I move to strike the last portion of the answer, I don't believe it was responsive and I don't believe there's a foundation for it, and I think it invades the province of the jury.

THE COURT: The last sentence was

non-responsive. It will be stricken.
BY MR. CIRESI:
Q. Doctor, do you know how broad the dissemination of this undertaking of a special responsibility was based on your review of the documents?
A. It was very broad. There's another document that said how many newspapers throughout the country. I think it went to every -- every newspaper -- or every city that had a population of about 50,000 people. So it was very broad.
Q. Can you direct your attention to Exhibit 14127 in volume two of the two volumes in front of you.
A. I have it.
Q. This is an agenda for the Tobacco Industry Research Committee meeting of January 18th, 1954. Have you reviewed this document, doctor?
A. I have, yes.
Q. Does it form part of the basis of your opinions in this case?
A. It does.
MR. CIRESI: Your Honor, we would offer Exhibit 14127.
MR. BERNICK: No objection, Your Honor.
THE COURT: Court will receive 14127.
MR. CIRESI: Publish it please. Thank you.

BY MR. CIRESI:
Q. That shows the agenda, Tobacco Industry Research Committee meeting, January 18th, 1954.
If we could put up the next page, please.
Doctor, I'd like to direct your attention to the first paragraph, "ADVERTISING.
"The Committee statement entitled, quote, A Frank Statement to Cigarette Smokers, end of quote, appeared in 448 newspapers, reaching a circulation of 43,245,000 in 258 cities. This included, with very few exceptions, all cities of 50,000 or more population, plus all plant or headquarters cities of Committee members. Total cost for newspaper space will be approximately $244,304. Cost of three press publications, paren, EDITOR AND PUBLISHER, comma, PUBLISHERS AUXILIARY and AMERICAN PRESS), will be approximately $2,113. Production costs will add $3,040 to this."
Is this the dissemination document of the Frank Statement that you had reference to?
A. It is.
Q. Now doctor, I'd like to move toward the anatomy and have you describe and explain for the ladies and gentlemen of the jury and His Honor that part of the anatomy, the body and brain, that we're going to be

dealing with during the course of your testimony. The first thing I'd like to do is have you work with

the model that we have in the courtroom.
MR. BERNICK: Your Honor, with the court's permission, will it be all right if I scoot around to the side?
THE COURT: Sure.
MR. BERNICK: Thank you.
BY MR. CIRESI:
Q. Doctor, if you could explain now, starting with the -- for inhalation, just a gross anatomy, mouth, trachea, et cetera, and describe it to the ladies and gentlemen of the jury. And make sure that the court can see also.
A. Okay. Well I'm going to start out by just starting with the -- kind of the upper airways, and then we'll go all the way down to the lungs, and then we'll come back and talk about the heart and kind of go through this. It's important to understand the way the physiology of this is because the delivery system for the drug we're talking about is inhalation. Different than intravenous. And when you give a drug intravenously, even though it sounds like it's very fast, it takes a longer time to get from here into the brain and the central nervous

system than it does if it's inhaled. So it's important to understand inhalation and how it works as far as the lungs are concerned.
So the first thing we'll do is I'm going to take the lungs out, I'm going to take the parts of the lungs out so we can see behind here. And I'm not a surgeon, so I may drop things every now and then. I won't say oops. That's a bad thing -- if you're a surgeon you should never say oops. The patient may be awake.
So we'll start up at the top in the mouth, and then this is the first part of the anatomy, this is the larynx or this is the voice box. You can feel it in your neck. When you inhale something, the inhalation goes down through the mouth and through the nose, through the windpipe, into the lungs. And when it goes into the lungs -- I'll pull this out so we can see behind the heart -- you can see the way the windpipe goes into here, branches into two branches, and then it branches out into the lungs like the branches of a tree. And think about it that way because every succeeding branch gets a little bit smaller, a little bit smaller, a little bit smaller, until it ends up in the tiny air sacks which are way out in the periphery of the lung. So when you inhale

something into your lungs, it goes into the lungs and eventually ends up in those small air sacks, and that's where the gas exchange takes place, like oxygen exchanging with carbon dioxide. Or if your -- if your furnace is not working correctly, carbon monoxide goes in this way and can come out into the lungs and into the -- into the bloodstream.

Now when things get inhaled and they're absorbed into the lungs, they're picked up by the blood vessels, and they're very small capillaries, and we'll show you more about that in a moment, very small capillaries, and these gases are picked up by these capillaries and are brought back to the heart.

Now when you think about the heart being in the middle here as being the receiver of all this, it comes back to the heart in the pulmonary veins. Veins come toward the heart, arteries go away from the heart. And this vein is an unusual vein because it's carrying oxygenated blood; it's a red vein. And that's the only place in the adult body that a vein is red, because it's carrying oxygenated blood.

And so once it gets back to the heart, then -- then the blood comes into the left side of the heart through the pulmonary vein into the -- into the left ventricle, and then it's pumped out of the left

ventricle. And the first arteries that come off of the heart are the coronary arteries. So the heart takes care of itself first, it feeds itself first. So the oxygenated blood goes to the heart first. And then the second two arteries that come off of here are off of the aorta. This is the aorta, which is the major blood vessel coming out of the heart, and then the next two arteries that come across -- or come off of the aorta are the carotid arteries, and the carotid arteries go up to the brain.

Over a third of the output of the heart in any heartbeat is delivered to the brain. It takes care of the computer first. Your -- your body takes care of -- of the brain first.

And because there's so much blood flowing to the heart, your mom probably told you when you were a kid that if you wanted to keep your feet warm during the winter, just wear a cap, and that's an insulating effect on the top of your head because so much of the heart -- so much of the blood comes out of the heart and goes to the brain and goes to the brain first.

The rest of the blood then goes down the back side of the -- of the center of the body and goes down into the aorta and it goes down to the rest of the body.

Now I've talked mainly about what happens if you inhale something and how it gets to the brain very quickly, because it goes into the lungs, then it goes to the left side of the heart, and then it's pumped directly out aorta to the brain to the rest of the body. What would happen if you had something pumped into the veins in your arm? And most people think about drugs and drug-delivery systems as being very, very bad if they're intravenously given, but that's a much slower way to get -- get a drug to the brain than it is by inhalation.

And the way that it goes is like this. I'll put

the heart back in; give that little transplant. So if you got -- you have -- if you have blood, an intravenous catheter or you give a drug intravenously in the arm, it goes up through the arm and then it comes into what we call the superior vena cava, which is this blue vein right here. It then goes into the right side of the heart, and then it's pumped to the lungs through the pulmonary arteries, which are blue here because the blood is going away from the heart but it hasn't got oxygen as yet. It then picks up oxygen and it comes back to the heart through the pulmonary veins, which come into the left side of the heart, and then they're pumped to the rest of the

body.

So it takes a lot longer to get from here to here, meaning from the arm intravenously to the brain, than it does from inhalation. It takes about five heart beats to get from here to here. And that's why the delivery system we're talking about, and the document just said -- I've forgotten what the exact words -- I -- I termed the cigarette the most efficient delivery form of nicotine that exists. It gets it from your hand to your brain faster than any other method.

Q. Doctor, you mentioned that once you have the lungs that are branching out, you said it's like a tree?

A. Uh-huh.

Q. Is there a term called alveoli?

A. Right, the -- I should have explained that. When you get in the -- the -- the windpipe, it here is called the trachea, and then when it branches into the two major branches it goes into the right and left main-stem bronchi here, and then as it continues to branch out and branch out and branch out further, you then go up into the alveoli, which are the small air sacks, which then is where the gas exchange takes place.

And it's an enormous surface area. And it's actually dependent upon how tall you are. The taller you are, the more surface area there is in the lung. Lung function tests, when we do those in patients, are different for people that are taller. So, for example, my lungs would probably cover -- if you were to lay them out flat, and these alveoli, which are the one-cell layer small air sacks, if you lay them out flat, my lungs would cover the better part of a football field just because of my height. So they're very, very large and they give us a lot of reserve, but they're also a very large surface area through which and on which drugs can be absorbed.

Q. Doctor, maybe you can -- could you maybe draw that and show the ladies and gentlemen?

A. Sure.

Q. If yours cover a football field, mine's probably

a handball court.
A. I wouldn't touch that.
Well it's probably -- I'm not a -- you have to bear with me. I can draw some things but not all. So we'll put your nose up here, chin here, then your mouth. And then it goes down into the right and left main-stem bronchial tubes, the major wind pipes as they go down into the lungs. And then as it goes

down it branches, and the further down into the lungs the branches of the tree get smaller and smaller and smaller until you get to the places where the gas exchange takes place. Now along the way there are -- there's a lining of the inside of the lungs, and the lining protects us, in the upper parts of the airways it protects us from things we might inhale. So if you're to look at the -- at the trachea or the bronchial tubes here, and if you look at it on a cross-section, like if you take a garden hose and cut it this way and look at the tube on end, it would be lined with -- with -- with epithelium that we call columnar epithelium because the cells are tall like columns, and on the tips of the columnar epithelium -- I'll just draw one of those cells over here -- on the tips of them are little things called cilia. And these columnar epithelia secrete mucous, and the mucous forms a little layer on top of these little cells, and that acts like fly paper. So if you have a particle that comes into the lungs, it gets stuck on the fly paper. And then the little cilia, the little hair-like projections, sweep the -- sweep the mucous toward the outside. And the best example I can give you is when you clear your throat or when you cough. When you clear your throat you go

(clearing-throat sound) and then you swallow, and what you've done is you've raised mucous from down in the lungs up closer to the esophagus, and then you swallow the mucous and get rid of anything that was trapped on this little mucous layer.
So the cilia move this way very rapidly as they push the mucous out, and then they relax and sweep. It's like a -- like a vacuum sweeper. And smokers have a real problem with this sometimes because there's such a thing as a smoker's cough, usually occurs in the morning, and the reason that that occurs is that these cilia are very sensitive to things that are chemicals. I know we heard a lot about chemicals yesterday that are in cigarette smoke. There are several chemicals in cigarette smoke that are called ciliotoxins, and what that means is they're toxic to these little cilia, these are very fine hair-like projections, and there are some things in cigarette smoke that will paralyze these little hair-like projections for as long as 45 minutes per cigarette. So that if a person smokes a pack a day, then the little cilia are basically

paralyzed all day long. And then overnight, as the effects wear off, then the cilia begin to be operational again, and the next morning the smoker

has the cough because they become active and begin to get the -- get the mucous out of -- out of the body.

As you go further and further down the tree, this lining becomes thinner and thinner and thinner until it gets to the very bottom, which is down here, and we'll draw an alveoli down here. At the very end of the system is what we call the terminal alveoli -- "terminal" not in the life-or-death sort of situation, but the last, "terminal" means the last of the -- of the alveoli. And these are the little fine hair-like projections that are at the bottom of the -- of this, and these are basically one cell layer thick. They're very fine, they're very delicate structures.

When air comes in this way, then there is an exchange of gases across these membranes, oxygen coming in this way going across this membrane, and right next to this membrane -- it's called the alveolar/capillary membrane -- is the capillary. And the capillary is kind of the last and the smallest of all the blood vessels. This little capillary then brings waste products like carbon dioxide back to this and then the exchange takes place. So that oxygen goes in, and carbon dioxide and other waste materials go out.

So this is the very end part of the -- where the -- where the gas exchange takes place, not only for oxygen and -- and carbon dioxide, but if your furnace isn't working, this is where -- this is where carbon monoxide gets in too, through this same system. And this is how nicotine gets in through -- through the system to be absorbed into the body.

Q. Is there anything on the lining of the lung, the epithelial lining of the lung, at the alveoli level?

A. Right. When you get down -- we've already lost the tall -- tall columnar epithelium, and the further down in the tracheal bronchial tree you get, the lining of the lungs get smaller and -- or thinner and thinner and thinner, but down here there is a -- there's a substance called surfactant which coats these very small -- this lining of the inside of the alveoli, and the main function of surfactant is to keep these little air sacks expanded. If you don't have that, then the pressures of breathing in and out would cause some of these very delicate structures to collapse. And so the surfactant is the main thing within the body as far as a -- of a structure that helps to keep the alveoli expanded so they don't collapse.

Now there are other things that keep the alveoli

expanded as well. When we take a deep breath or sigh, then it forces air into areas of the lungs that may not be getting all the air that they had been getting from previous breaths. In fact when you sigh, when you sigh, that's a -- that's an automatic thing that your body does to make sure there's enough air getting to all areas of the lungs so that little air sacks that may be trying to collapse a little bit will then be expanded and so they'll continue to function. Because when you change your body position, if you're laying on one side or the other, it changes the dynamics in here so that there's -- the blood flow and the airflow changes with position. So it's important to keep all the air sacks open as best we can.

When we have a person on a ventilator in the intensive care unit, we have a sigh mechanism on the machine, so that every so often we'll have them to take -- the machine will take a deeper breath for them so it will keep all the little air sacks expanding.

Q. Thank you, doctor.

I'd like to talk a little built about the brain, doctor.

A. Okay.

Q. If we could use the model once again.

A. Okay.

Q. Can you show the route to the brain from the lung?

A. Okay. I kind of went over a little of that, but I'll keep the brain down here.

The route to the brain, as I think we've already talked a little bit about, is when you inhale some substance, it goes into the -- the -- the pulmonary system, delivered back to the -- to the heart via the pulmonary vein, veins come to the heart, into the left ventricle, and then out the aorta up into the carotid arteries, which are the main arteries? You can feel those in your neck, those are the ones that you can feel right in your neck, and then it goes to the brain.

Now when it gets to the brain, the area we're focusing on when it comes to nicotine and its effect on the pleasure and reward part of the brain is called the mesolimbic system. It's kind of a whole area in the midbrain. This is the front part of the brain, which is up here, this is the cerebellum which is the part that has to do with the balance, this is the brain stem, this has to do with the respiratory centers and so on, and this is an area called the

midbrain, and in the midbrain are various other structures. One is called the nucleus accumbens, and that's the area of the brain where dopamine is

released in response to high levels of nicotine when they're administered, especially by the system we're talking about, inhalation. And dopamine is released, and that's where the pleasure and reward system comes into play, just like it does with cocaine and opiates and other drugs of addiction.

Q. Doctor, you were mentioning when you were testifying that one of the ways to determine the nicotine level is by measuring blood levels in smokers,?

A. Correct.

Q. Is there a way you can illustrate that with regard to the blood levels based on the pathways to the brain?

A. I'll have to use this one.

When we think about the blood levels that you have in your -- in your bloodstream from -- from a drug, then you can measure, and what we're going to talk about right now is nicotine levels that you can measure in the bloodstream. And so I'm going to draw over on this side just a straight line, and these will be the nicotine levels in the blood. I'll just

label it blood nicotine levels.

THE WITNESS: Can you see okay?

THE COURT: Fine.

A. And I'm going to draw basically three little drawings. One has to do with the arterial levels, your artery levels in here, I'll also draw one that will show the venous levels that you might measure out of the veins in the system, and I'll also show you the venous levels that you might get from a nicotine patch, which is probably the easiest thing to relate to. And the nicotine patch, the levels that you get from the nicotine patch take a real long way to get to the brain because they go through the skin, it's absorbed into the small veins and then eventually gets into bigger veins and then gets into the heart, the right side of the heart, pumped to the lungs, then pumped to the left side of the heart before it ever gets to the brain. So the venous levels, the levels in the veins of nicotine patches, is basically the same as we see in the artery levels. They're basically the same.

When you have a cigarette that's used and smoked, inhaled, it has a shorter route to the brain, and the arterial levels can be extraordinarily high. I'm going to draw them like this. I'll put some

numbers on them in a minute that you can understand or relate to. And this would be like you're having one cigarette an hour, which is a fairly typical pattern for people when they're smoking. And so the levels here are variable from person to person; it depends on how deeply a person inhales, how long they hold their breath, as well as other factors. And so these levels could be as high as 80 or so nanograms

per ml. Nanograms is a small unit. Ml is milliliters of blood. It's just a blood test we would do, get a standard readout.

If you were to look at the -- the same pattern that would be occurring in the veins, if you were to measure the veins on a smoker smoking a cigarette, you had the measures in the artery here and also taking measures in the -- in the -- in the venous system, they would also go up and down in this spike-and-trough manner, but they'd be delayed and they wouldn't go nearly as high.

So they might have -- you might have levels of 20 nanograms per ml or something on that order. So three or four times higher levels in the brain when you inhale something that's -- that's really the -- the shortest route to getting from here to here, is inhalation, and these levels can be very, very high.

Now if you were to put on a nicotine patch and you were to put on a nicotine patch that may be a 21-milligram nicotine patch, it's a very slow delivery system. It doesn't get into the system very quickly at all. And the levels take a long time for them to go up and they don't ever get very high. If they get to be, you know, 17 to 20 nanograms per ml, that would be a pretty good -- pretty good size effect, and most of the time they're much lower than that. The venous levels are the same as the arterial levels because they're delivered through the skin. And these would be very -- this would be very variable between smokers and individuals. Some will have a much higher level than others depending upon how they handle the drug.

So just to re-orient you a little bit, this would be smoking one cigarette per hour. And if you were to break this down even further as -- as a puff off of each cigarette, each puff would have a little -- little blip on this curve, but that would -- you'd have to measure these a lot and very frequently in order to be able to detect that. The whole point is that it's a very long distance from here to here, the spikes are very high, and the effects that they have on the brain are very

profound.

Q. What's the significance of getting the nicotine to the brain faster with the shorter pathway of inhalation versus a venous pathway?

A. When you're talking about a drug of dependence or a drug of addiction, the faster that you can get it to the brain and in the higher concentrations, the more the addictive potential, the more potential it has for addiction.

And the analogy I would use would be crack cocaine. When you snort cocaine, it goes in through the nose and it goes into the venous circulation around the nose, and it comes into the -- the

superior vena cava, that blue vein coming into the right side of the heart, it's then pumped to the lungs and then back to -- to the left side of the heart, and then it's pumped to the rest of the body and to the brain. So that's what happens when you snort cocaine.

A more efficient way as far as a drug of addiction to get cocaine to the brain faster is to inhale it. Crack cocaine is the way of doing that. And so crack cocaine actually looks very similar to this as far as the blood levels are concerned with -- with inhalation versus snorting. They're -- they're

very, very similar as far as the drugs themselves are concerned. And inhalation is the most efficient way of getting the drug of abuse to the brain faster.

Q. Thank you, doctor. Take the witness stand again, please.

Doctor, could you direct your attention again to volume one of the books in front of you.

A. Okay.

Q. And if you could, please, turn to Exhibit 12392.

A. Okay.

Q. This is a memorandum of BATCo dated August 8th, nineteen ninety -- I'm sorry, August 7th, 1991, to Mr. B. D. Bramley, who was chairman of BATCo, from Linda Rudge, R-u-d-g-e, information scientist, with carbon copies to an Alan Hurd, H-u-r-d, senior research executive, and Richard E. Thornton, RET are his initials, a scientific advisor.

Is this one of the documents that you've reviewed in this case?

A. It is.

MR. CIRESI: Your Honor, we would offer Exhibit 12392.

MR. BERNICK: No objection.

THE COURT: Court will receive Exhibit 12392.

BY MR. CIRESI:

Q. There we see the memorandum "Smoking cessation methods," and the date is in the upper left-hand corner, August 7th, 1991, and it shows over on the right side that it's been received on August 8th, 1991 by Mr. B. D. Bramley, and you see the -- over in the left-hand column or side of the document it's the author, Linda Rudge, and below that the initials of Mr. Hurd and Mr. Thornton.

Now doctor, I want to just direct your attention to the second paragraph of this where Ms. Rudge states as follows: "Overall, most methods have achieved, at best, only moderate success because they cannot imitate the unique property of inhaled cigarette, the delivery of unchanged nicotine to the brain occurring a few seconds after taking a puff."

Now is this illustrative of the principles that you were just testifying to, doctor?

A. It is, yes.
Q. Did you see other documents of the defendants which also manifested this knowledge?
A. There were many of them.
Q. Can you direct your attention to Exhibit 12390.
A. Say it again.
Q. 12390. It's the one immediately preceding.

Do you have it, doctor?
A. Yes.
Q. Is this another document that you reviewed?
A. It is. Yes, it is.
Q. So this is again a BATCo Ltd. document, the date of it is February 28th, 1992, which you can ascertain by going to the second-to-the-last page of the document, which is a response to the document, and it gives the date of the document there as 2-28-92. Do you see that?
A. I do.
MR. CIRESI: Your Honor, we would offer Exhibit 12390.
MR. BERNICK: No objection.
THE COURT: Court will receive 12390.
BY MR. CIRESI:
Q. Doctor, the subject matter of this document is transdermal nicotine. What is transdermal nicotine?
A. It's the nicotine patch. "Transdermal" just means across the skin. And this is reference to nicotine patch therapy.
Q. Two questions are asked on this page. First one is under the -- or next to the initial a) at the top, "Whether this is a significant technical advance and whether it is likely to be developed into a salable

product for mass markers -- markets." And then it goes down to b) which says, "If so, does it represent a significant threat to the tobacco industry?"
In response to question a), you'll see it right above the letter b), the writer concludes that "From the technical standpoint -- viewpoint mass production of this product is possible."
And I want to direct your attention to that portion of the memo in which the author gives her response -- or gives the response to whether it would represent a significant threat to the tobacco industry.
"Apart from the fact that these products are used in therapy to break the smoking habit and even when thus applied have so far not achieved any significant success rates, dash, no, exclamation point.
"As the pharmacodynamics of nicotine absorption vary widely compared with smoking, e.g., a far longer time taken for absorption through the skin, far longer times needed to transport the nicotine to the central nervous system and thus to form a nicotine plateau, the rapidly achieved stimulating or soothing

effect of nicotine which the smoker wants cannot be achieved. Such a product can thus not be a

substitute for the cigarette."

Now what's being reported here is that which you drew on the bright board?

A. Yes, it is.

Q. Continue to direct your attention to Exhibit -- or page 828 -- and I'm referring to the numbers on the right-hand side, the last three digits.

A. Okay.

Q. It would be -- it would be the third page in.

In this paragraph is the author talking about how the pharmacological effects of application differ quite clearly from nicotine intake via smoking?

A. That's what it says.

Q. Okay. And in this paragraph does the author set forth the short pathway versus a longer pathway to the brain of smoking versus transdermal?

A. Yes, they do.

Q. And is that consistent with what you were just describing to the ladies and gentlemen of the jury?

A. It is.

Q. Now in this document, if you go to page 831, last three digits, they cite you and one of your articles?

A. Yes. It's number eight.

Q. Okay. Can you go to Exhibit -- or excuse me,

page 834, again last three Bates numbers.

A. Okay.

Q. And is that a diagram such as the one you just drew for the ladies and gentlemen of the jury?

A. It is. There's some variability, but it's very -- very -- very much what I just drew, yes.

Q. And finally with regard to this document, can you go to page 835, which shows the rate of absorption spectrum from rapid absorption down to slow absorption, and it shows inhaled smoke at the highest level there, with a nicotine skin patch being down at the bottom. Do you see that?

A. I do.

Q. Okay. And they have tobacco products on one side and new delivery systems of nicotine on the other; correct?

A. Correct.

Q. And is that consistent with what you were describing to the ladies and gentlemen of the jury?

A. It is.

Q. Doctor, you've talked about receptors in the brain, if the arterial levels of nicotine are high, there's an effect on brain receptors.

A. Uh-huh.

Q. Could you describe what a brain receptor is?

A. There are many different types of brain receptors, and -- and when -- in this situation we're talking about, a receptor that's called the acetylcholine receptor. Acetylcholine is a chemical substance, it's a naturally-occurring chemical substance in the body, and acetylcholine is structurally fairly similar to nicotine, so over the years as -- as people have experimented with these receptors that are in the brain, this one has become known as a nicotinic acetylcholine receptor because nicotine can activate the receptor just like acetylcholine can.

Receptors are located on the surface of the neurons or the nerve cells, but they're also located in other parts of the body as well. You have receptors or on muscle, you have receptors -- because receptors are basically the lock to a cell, and then the key to unlock the cell is the neurotransmitter. In this case it would be acetylcholine or nicotine would activate the receptor, which then activates the nerve cell to do whatever it's going to do.

So there -- basically receptors are -- are kind of like the lock and the neurotransmitter is like the key that opens up the receptor to then allow the neuron or the nerve cell to be activated. And when

we're talking about the neurons that are in the areas of the brain that I mentioned earlier, the thing called the nucleus accumbens, that's an area of the brain which we know when substances are delivered to it like cocaine or -- or opiates or nicotine, it will activate those neurons to produce dopamine. And dopamine has to do with the addictive cycle because dopamine has to do with pleasure and reward.

Q. All right. So the neurotransmitter in this case would be the nicotine?

A. That's correct.

Q. And that activates the receptor?

A. It does.

Q. And that would then trigger it -- trigger the nerve cell?

A. Correct.

Q. Okay. Which then triggers the release of dopamine?

A. That's right.

Q. Are you familiar, doctor, with the term "upregulation?"

A. I am.

Q. And what is that?

A. When -- when you have a drug that is being delivered to an area where there are neuroreceptors

in high concentrations and delivered frequently, usually that means to the cells that there is not -- not as much of a need for as many of these receptors to be -- to be present on the surface of the nerve

cells. In the case of nicotine, which is really a unique substance, when nicotine is delivered in high levels like it is in cigarette smoke, there is a process called upregulation, so these nerve receptors or the neuroreceptors that are in these areas of the brain, with this exposure to nicotine over time, they actually end up with more of them. They're upregulated in that there ends up being more of them and they're more active. So that with exposure, then, of nicotine to those areas of the brain, then the neurons can be more active and they can pour out more of the substance that they might be secreting, like dopamine.

So when upregulation occurs, that has to do with the addictive cycle because when these -- the -- when there are more of these nerve receptors or neuroreceptors present in those areas of the brain and then you stop smoking and you stop exposing them to the nicotine that is normally activating them, then withdrawal symptoms occur. So it has to do with the addictive cycle that we see in patients that are

dependent on nicotine.

Q. If the nicotine is withdrawn or you cease providing the nicotine, what if any effect is there on the individual?

A. Well first of all there's withdrawal symptoms that occur: irritability, anxiety, frustration, inability to concentrate.

When I stopped smoking the people in the unit, one of them came to me during middle of all of this and said, "Hurt, you got to start smoking again. You're just such a crab, you're too tough to be around. I don't want to insult you, but please go get a pack of cigarettes and start smoking again."

So the emotional part of this can be very, very significant. The other parts are -- are -- can be even more severe. Depression can occur in people who stop smoking. So the neurochemistry of all this can be very profound. We've had patients who have become profoundly depressed and had to be hospitalized when they would become -- after -- after stopping smoking. We've had patients who had to have electroconvulsive therapy, ECT, when they become very depressed after stopping smoke. We've had people admitted to the hospital because of severe anxiety after stopping smoking.

So these reactions that occur up here that are mediated by these chemicals are very, very profound. They can be mild, people can have mild symptoms as well. But they're mediated through the chemical system that's in the brain that have to do with the neurotransmitters and the things that they release.

Q. You've described upregulation. Is there a term known as "downregulation?"

A. There is.

Q. And what is that, doctor?
A. It's the exact process in reverse. If a person stops person and is no longer having these very high spikes of nicotine, then these nerve receptors, the neuroreceptors, begin to downregulate and they -- they actually reduce the number in these areas of the brain, so that over time a person can get back to kind of the way that they were to begin with.
However, once exposed to these very high levels of nicotine, some of those receptors I don't think ever forget, because -- and patients tell us this all the time. "I stopped smoking three or four years ago and then I had a crisis situation, and all of a sudden I thought to myself I can have one cigarette. I had a cigarette, and within -- within two days I was back smoking two packs a day." Because the nerve

receptors that are there, once sensitized by these high levels of nicotine administered via cigarettes 20 or 30 times a day for 20 or 30 years, even though they may be downregulated, I'm not sure that they ever forget.
Q. Doctor, can you once again turn to volume two and please turn to Exhibit 13359.
A. Okay.
Q. This is a document entitled "NICOTINE PHARMACOLOGY AND NEURODEGENERATIVE DISEASES PROGRAM (NPND)/POSITIVE ASPECTS OF NICOTINE." It's an RJR document produced by RJR Tobacco Company and dated May 25th, 1994.
Is this one of the documents you've reviewed in this action?
A. It is.
MR. CIRESI: Your Honor, we would offer Exhibit 13359.
MR. BERNICK: No objection, Your Honor.
THE COURT: Court will receive 13359.
BY MR. CIRESI:
Q. You see on the front page the project name, the authors, and the date of May 25th, 1994. Now was this document published by RJR after the lawsuit was filed?

A. "Published" like in the medical literature?
Q. Yes.
A. There's an article that -- that is part of this document, it's not the whole -- whole document, but part of it's been reported, yes.
Q. Now under OBJECTIVES/SIGNIFICANCE -- and I just want to read the first part of that: "The tobacco alkaloid nicotine and the brain neurotransmitter acetylcholine have been shown to bind with high affinity to brain preparations from various species including humans. Chronic activation of all brain receptors studied to date results in a slowly-developing decrease in their number. The only documented exception is the brain nicotinic receptor

whose activation results in an increase in receptor number."

What's being described there?

A. Upregulation.

Q. And as you continue through that paragraph, down at the bottom it says, "In other words, silent receptors designed otherwise to be degraded will in the presence of nicotine convert into the high affinity state, i.e., the state stabilized in the presence of nicotine." What is being described there?

A. Well there -- there are probably two mechanisms by which upregulation occurs. Some of the less-active neuroreceptors can be more activated. The other way that they increase in their number is to lengthen their life-span, so nicotine exposure over time will make them remain there longer. There's a normal life cycle for receptors in the brain like receptors in other places, so they don't just stay there forever like that. So there's kind of two ways that up regulations occur. One is the recruitment of lesser-active neuroreceptors to more activate them, but also to lengthen their life-span. And so the net result is you end up with more.

Q. Doctor, can you turn, then, in the same volume to Exhibit 13534, which is the next exhibit.

THE COURT: Counsel, why don't we take a short recess at this time.

THE CLERK: Court stands in recess.

(Recess taken.)

THE CLERK: All rise.

(Jury enters the courtroom.)

THE CLERK: Please be seated.

MR. CIRESI: Your Honor, for illustrative purposes, I'd like to offer the model, which is Exhibit 30110, the three charts which Dr. Hurt drew,

Exhibit 25001 is the upper bronchial tract, Exhibit 25002 is a drawing of the alveoli, and Exhibit 25003 which showed nicotine -- nicotine concentration levels in blood.

MR. BERNICK: No objection.

THE COURT: Court will receive 30110, 25001, 25002, 25003.

BY MR. CIRESI:

Q. Doctor, you have in front of you Exhibit 13534?

A. Yes.

Q. This is a B.A.T exhibit which is dated March 22nd, 1984 entitled "RECEPTORS FOR NICOTINE IN THE CENTRAL NERVOUS SYSTEM, I RADIOLIGAND BINDING STUDIES." Is this one of the documents that you reviewed in preparation for your testimony?

A. It is.

Q. And this forms --

Does this document form part of the basis for your opinion?

A. Yes, it does.
MR. CIRESI: Your Honor, we would offer Exhibit 13534.
MR. BERNICK: No objection.
THE COURT: Court will receive 13534.
MR. CIRESI: Place the title page on the

overhead projector which shows the title which I've just read into the record, and also the date of March 22nd, 1984, shows that it was issued by C. I. Ayers and the author was Wilma W. Templeton, went to group leader G. A. Read and the distribution list included a number of other individuals at B.A.T, including doctors and others in their laboratories.
BY MR. CIRESI:
Q. Doctor, can you turn to page 998 of the exhibit.
A. Okay.
Q. And again I'm referring to the last three Bates numbers.
A. Okay.
Q. Now this is an executive summary of the document?
A. Yes, it is.
Q. And does it in the first two paragraphs state the purpose of the study?
A. Yes. Talks about how nicotine derived from cigarette smoke can interact with the body, particularly the centers in the brain.
Q. And does the report then -- does -- strike that.
Does it go on to state that the report will describe in detail the development and application of techniques to identify and characterize regions

within the brain tissue where nicotine combined to elicit a pharmacological response?
A. That's what it says.
Q. The Surgeon General's report on nicotine, finding it addictive, finding cigarettes addictive, what year was that?
A. 1988.
Q. So this would have been, then, four years before that?
A. That's correct.
Q. Can you turn to the next page, doctor, which is Exhibit 999 -- sorry, page 999.
A. Okay, I got it.
Q. That's the technical abstract?
A. Yes.
Q. Okay. And what is being described there in the first three paragraphs?
A. Well it talks about the -- the nicotine binding to certain areas of the brain. They say the least two types of sites that are a high affinity site, which would be a site that would be more attractive to nicotine, and they describe that as the classical nicotine cholinergic profile, which has to do with the receptors we talked about before, the

acetylcholine receptors, that's what acetylcholine

has to do. So it talks about the nicotine receptors and how nicotine interfaces with them.
Q. And can you turn to what's called the introduction page that bears the last three Bates numbers 001.
A. Correct.
Q. And maybe we could show the Bates numbers so the ladies and gentlemen of the jury know what we're referring to when we say that during the trial. So we'll refer to the last three so we don't have to read seven or eight digits.
A. Okay.
THE COURT: Counsel -- counsel, I wonder if for the benefit of the jury you could explain what a Bates number is.
MR. CIRESI: I could, Your Honor. I'll try.
THE COURT: I think we -- I think we all agree on that.
MR. CIRESI: A Bates number is a number that's applied to a document when it's discovered in litigation so that you know where the document came from and what number it is. So if I were producing documents on behalf of the state of Minnesota, or any of the defendants' lawyers were producing documents

on behalf of the defendants, we put a Bates number on that so we can track that document as to when it was produced. And if we want to go up and retrieve it, we're able to go to retrieve that numbered page. So if it was a ten-page document, let's assume, and we were just starting, it might be page -- the Bates number may be one through ten, the last three digits.
And you'll also see for some of the defendants there will be initials in front of it, so some defendants put their initials in front, and we'll identify those for you as we go through so you know what those are when you see them on the documents.
THE COURT: Thank you, counsel.
MR. CIRESI: Thank you, Your Honor.
BY MR. CIRESI:
Q. Doctor, directing your attention, then, on page one, the second paragraph, it says, "Several explanations of smoking motivation allow no role for nicotine; for example that it is rewarding in terms of taste, smell or irritation, or that it is simply an activity. However, it is known that smokers rarely use products, paren, such as herb-filled cigarettes, close paren, which contain no nicotine. Likewise, there has been, paren, and possibly still is, close paren, consumer resistance to low tar, and

hence low nicotine, cigarettes. Additionally, smokers take more frequent and larger puffs from cigarettes which are lower in tar and nicotine yield than their normal brand, although other, contradictory reports have also been made. Taken together, the evidence suggests that self-administration of nicotine may be the primary motivation for smoking."

Now I specifically want to refer you to the sentence there that says "Additionally, smokers take more frequent and larger puffs from cigarettes which are lower in tar and nicotine yield...." What is that referring to, doctor?

A. Well it's referring to compensation, the term we use when a person may be smoking a -- a cigarette that is designed to deliver lower tar and lower nicotine levels when it's smoked by the Federal Trade Commission smoking machine, which gives a certain level in the smoke. But cigarettes don't smoke like the machine smokes. This machine has a certain depth of inhalation, a certain number of inhalations per cigarette, but smokers smoke differently than that.

And so this refers to compensation, which would mean that a person may take a larger puff, inhale

deeper, hold their breath longer, and therefore, even from a low delivery product, can extract basically the same amount of nicotine that you can get from a regular cigarette. And so what they're mentioning here has to do with smoking for a level of nicotine in the brain which is what -- what -- what happens in people who are smokers.

So even though they have a low -- low tar, low delivery product, the person will smoke it differently in order to get the same level in the brain that they would with a different type of product.

Q. The last paragraph states, "When smoke is inhaled, nicotine is introduced to the lungs. The vast surface area of the lungs, coupled with the rich blood supply to the alveoli, ensure that nicotine is rapidly and efficiently absorbed. The nicotine is then distributed by the body -- by the blood," excuse me, "to all parts of the body. In its" -- it says "unionized form "--

A. Unionized. Unionized.

Q. Unionized. I'm sorry, thank you. "In its unionized form, nicotine is extremely fat soluble and so can penetrate through cell membranes. As free nicotine passes from the blood (thus upsetting the

equilibrium between unionized and ionized compound) nicotine present as salts forms free nicotine base."

What is being referred to in that paragraph?

A. Well really the first part has to do with the surface area of the lung, and then the second part

has to do with free nicotine. In this case we're talking about free base nicotine which was mentioned yesterday. Free base nicotine is the form of nicotine that has the ability to go across these biological membranes at a much faster rate than other forms of nicotine. Basically there are three forms of nicotine that can occur with hydrogen ions attached to it or not, and the one we're talking about here is called a free base nicotine which has no hydrogen ions attached to it, so it's a smaller molecule and has more activity, can go across biological membranes very, very quickly.

And I'd just add to that, the speed with which nicotine gets to the brain is really important when it comes to its addictive potential, and so delivering it in the lungs, first of all, is very important, but then if you can do something to speed up the trans -- transmission of the nicotine across that little membrane, the -- the on cell thick membrane in the alveoli, anything you do to speed the

process across that will speed it up as far as getting to high concentrations in the brain, and that also has to do with its addictive potential.

Q. Thank you, doctor.

Looking down a little bit on page two, the first sentence of the first full paragraph starting with the word "Primarily...." "Primarily, nicotine is taken for its effects on the CNS...." What's the CNS?

A. Central nervous system.

Q. Now this is a B.A.T document, but is this statement consistent with statements you've found in the other defendants' documents?

A. That's correct.

Q. Doctor, I'd now like you to turn to the animations that you have on the monitor in front of you --

A. Okay.

Q. -- which will illustratively depict some of the principles that we've been talking about here this afternoon and what you showed on the model and what these documents had reference to. And I'm going to switch -- I hope this works. Did we switch over to the Z Axis? I'm going to switch the control panel from me to you so you should have control, and I'd

first like you to deal with the non-smoker.

And I might, if I could, Your Honor, let the jury know that because of the overhead lights, it's best if you look at these two monitors on either side of you. They'll give you a better picture than the overhead over there.

A. Well the first thing I'll do is go through the physiology of how this works in a person who is a non-smoker, "physiology" meaning just the way the body functions. And we'll talk first of all about

just normal respiration, the way the lung functions, the way the heart functions and the way the brain functions, and then we'll do it all over again with reference to smokers and how this occurs in smokers.

So we'll first of all do a person who's a non-smoker and we'll just go through and I'll show you as we go through the different body structures and how this works. I've kind of already drawn this out for you, but we'll -- we'll do -- do more as we go through.

So just to re-orient you to the body structures that are important, the trachea is here, and the air comes in through the trachea and goes down into the lungs. The heart, obviously, is important in the middle. We put the intestines, stomach and other

organs on here just so you could have a point of reference. This is the stomach, large intestines, small intestines down here. We took the liver out, which would normally be there, because it's so big and kind of obstructs things. So this is kind of the basic orientation of the body in the trunk. And as you can see, the veins are over on the side and the arteries are also here, and then the two main arteries going to the brain are the carotid arteries, which was named up here. So we'll just go through at kind of slow-motion speed so you can see how this works, and just to demonstrate to you the way the body functions.

It takes a little while to get started in this one.

MR. BERNICK: Your Honor, to avoid interrupting later on, for background we have no objection if there is a statement, but at some point in the tutorial I guess we would expect there to be questions and answers in the traditional format so that if there are areas that we would have an objection, we'd have an opportunity to state that objection.

MR. CIRESI: Well, Your Honor, I'd have to interrupt the doctor as he's going step by step. I

intend to ask -- allow him to describe this. If they have an objection to that, I have no objection to their standing up and say they object to something he said.

THE COURT: Well listen, why don't we start and see -- I don't want just a complete narrative.

MR. CIRESI: No, I understand.

THE COURT: This is a question-and-answer process. But why don't we start and see how it goes.

THE WITNESS: So can I proceed?

THE COURT: Please.

THE WITNESS: Okay.

A. So you can see the lungs are moving up and down as the air goes in and the air comes out, and pretty soon he'll turn around and you can see a side view.

And up in the upper part of this is the nose and the mouth. The esophagus is behind.

And I might just stop here just a second. We talked about this as being the voice box. This is the larynx, and the esophagus is right behind here, and this is the area where there's a little flap that covers over the trachea to protect the lungs. If you ever swallow at the same time you're taking a breath, you choke, and that's what happens; you get particles down there the trachea and that causes you to cough.

Q. What is that called, doctor, the epi --
A. Epiglottis over -- overlies the glottis. The glottis is the opening.

So I think I've drawn this for you as far as the lungs are concerned. This is just depicting the air as it's coming in and coming out. The structure -- as I mentioned here, the lungs are these two, two larger organs. The heart is in the middle. The main bronchi, which are the ones that come out into the lungs and make the smaller branches as they go out, are depicted here on both sides. This is the superior vena cava. This is the -- the vessel that brings blood back to the heart from the arms and from the head. And this is the inferior vena cava, which brings blood back from the legs and -- and below -- below the diaphragm. And so you can see there's a lot of blood coming back into the right side of the heart and mixing together and therefore diluting out anything that might be injected.

So we talked about this before. If you were to inject a drug over here into the veins, it comes up here and ends up in that -- that big mixing vat, if you will, of the blood coming from the lower part as well as the upper part of the heart. So if you give a -- give a drug intravenously, automatically it's

going to be diluted by the other blood that's -- that's already present.
Q. Doctor, let me ask you one thing. You were showing the, if you will, the limbs of the bronchi?
A. Yes.
Q. Can we see the alveoli here?
A. No, no. The alveoli are on there, but you can't see them. And we'll have another one in a minute that will focus down on the alveoli so you can see them. This is really just giving an over -- this is kind of a view from 50,000 feet sort of. So we'll get down to lower levels as we go along.

And this is a slower speed, so the heart is not going as fast as it would be at realtime, which we'll come to in just a moment.
Q. How far do the lungs extend down?
A. Well the lungs extend on me, would extend down -- way down to here. In fact on the back side they come down below the ribs. So the lungs are very large, and when they are fully expanded they go way

down. If you've ever seen anybody that's had surgery for their lungs, the incision may be way back down on the back side.

Okay. Then let's go and speed this up a little bit and that -- then you can see this whole

run-through in realtime. You can already see the heart is beating faster. This is about 70 beats per minute, so this would be at resting state for most individuals, depending on how good a shape you're in. When you take an inhalation, your lungs actually go down because the lungs are filling up with the air.

Now this shows all the air coming in and going out. There probably is residual air that's in there, left in there to keep the lungs expanded. And you can see up here is the aorta and then these are the -- the areas of the aorta that branch into the carotid arteries. So the blood comes in and goes out to the arteries, to the brain.

So then we should move to the lung itself, and then we'll focus down on the alveoli so that you can see the alveoli and how they work. So this will focus in on an area of the lung, and it will bring up a section of the lung so that you can see what -- what a section of the lung looks like. And you can see it's kind of a honeycomb-looking structure when you cut across it like this. So each one of these little air sacks is a series of air sacks, and when a person gets emphysema, then these little air sacks are ruptured and you lose a lot of this surface area that's present in the lungs.

And then we'll go down and focus down even further into the inside of the lungs so that you can see what happens in these little air sacks as we go down further. This is labeled properly: the bronchus, the alveoli. And then as we focus down further, as this becomes the last bronchus, the -- the terminal bronchus if you will, you can see there's a lot of air sacks associated with the terminal bronchus.

Q. Doctor, can you stop right there? Is each one of these intended to depict an air sack?

A. Correct. Each one of --

Like this one, we're down now to a level where you can actually see, this would be a little air sack. So there's a tube on the inside of here coming into this little air sack, and what's depicted on the outside are the little vessels, the very small vessels that are one cell layer thick. And so the blue ones mean that there is no oxygen -- or less oxygen in those, and when the oxygen is picked up by those vessels, then they become red, and that's where the oxygen exchange takes place, and that's where the gas exchange for oxygen, carbon dioxide, carbon monoxide, and in this case nicotine also takes place there.

Q. Doctor, what is the size of the membrane of the lung as contrasted with other membranes in the body?
A. Well it's --
When you get down to this level, it's a very thin membrane because gases have to diffuse across it. That's -- the function of the lung is to allow oxygen to diffuse back and forth very easily. So when you get down to this level, we're talking about a single cell layer thick, and the -- the other side of the equation is the capillary, which also is a single cell layer thick. And so it's a very thin, very delicate membrane that allows for the gas exchange.
So this shows the inside of an alveoli, and then these are the two ends of the air -- air tubes or the bronchial tubes that come into the alveoli, and then this surface area is -- as you can see, is very large, and there are millions of these air sacks in the lungs. That's why I said earlier, if you were to lay my -- my lungs out flat, just with this being the surface area you're laying out, it would be a very large surface area. So fortunately for us, we come with a lot of extra equipment, if you will, when it comes to our lungs, so that some damage can be done to them but a person can continue to function fairly

well even though there may be some damage to the air sacks because we have so many in reserve.
And then we're going to go right down to -- to this membrane that Mr. Ciresi was mentioning. This is the alveolar capillary membrane, and right here is what we call the epithelial surface. "Epithelial" means on the outside. So if you think about this, even though it's inside your body, it's exposed to air that's coming from outside, and that's really all it's exposed to.
And then this little membrane on the inside is called the endothelial or inside membrane or surface, and the two together make up what we call the alveolar capillary membrane, alveolus in here and capillary over here.
These are the red blood cells, and as you can see there's oxygen coming this way and carbon dioxide coming out. And this is a normal gas exchange that takes place in the body.
Now if we go to speed this up a little bit as far as the realtime is concerned, it looks like this and it's a lot faster. And again the heart's beating around 70 times per minute and the respiratory rate is around 15 or 16 times per minute. So then that takes care of the way the lungs work.

And then when you have the red blood cells

coming from the -- the small capillaries over here feeding into the larger -- larger ones, and then they become larger and larger and then they end up being, like on the model, the pulmonary vein which comes back to the heart, the red vein, and that's again the only part of the body in adults where there is red blood or oxygenated blood carried by a vein, is in the pulmonary vein. So then that comes back to the left side of the heart and then goes from the left atrium to the left ventricle and then is pumped directly out to the coronary arteries and then to the brain through the carotid arteries.

So really, the short way to get into the system is through the pulmonary circulation. It's basically a faster way to get a drug to the central nervous system.

Q. Could you go back, doctor, to the overall anatomy and show the venous route, I mean just by using the gross anatomy that we had?

A. Okay.

Q. Just show the longer route, if you will, as opposed to the shorter route.

A. Okay. That's probably easily done here.

So again the veins, if you put -- if you put a

drug into a vein intravenously over here, just with a needle, the blood has to go all the way up here and all the way down to here. And as I've already said, we end up with blood being mixed together from other parts of the body, so automatically it gets diluted so the concentration is less. And then it comes into the right side of the heart, then it is pumped to the lungs through the pulmonary arteries, and it goes through the same dynamics that happen when you inhale something. But it's already had a lot of -- lot of time spent in the body before it gets to that part. So once it gets to the lungs, then it will go out as fast as it would if it were inhaled, but it's already diluted, it's already mixed in with the rest of the blood, and so the concentration is much lower.

So not only is inhalation faster, the concentrations are much higher for comparable doses even if you give it intravenously. And the tendency is for people to think about drug-delivery systems by intravenous injection being kind of the -- the most efficient way to deliver a drug, and it really isn't. Inhalation is.

Q. Doctor, let me ask you one thing before you go on. When a physician is treating a patient and there's going to be a prescription drug given, be it

in the hospital or an outpatient basis, how do you know what dose to give to a given patient?

A. Depends on which drug you're talking about. If it's a -- if it's a drug that has to do with heart function, you might give a dose based on the amount of drug, like in milligrams per kilogram body weight.

The body weight of the individual has a lot to do with their -- the way that they would -- would be able to distribute a drug. Other -- other ways of doing it are like check a blood level or have a blood level. Like in diabetics, we would administer insulin based upon what their blood sugar is.

So it really depends on which drug it is as far as figuring out what dose to use.

Q. Who determines that dose?

A. Who determines it?

Q. Yeah.

A. The physician does, in cooperation with the patient. We try to figure out if there is something unusual about their situation, if they have liver disease or other diseases that might change the way the metabolism of a drug would be handled, and we need to talk to the patient about that and get their -- get their -- at least take their history and understand what's going on with them.

Q. Okay. And then how does that differ from a cigarette dose of nicotine?

A. Well a cigarette is -- is a -- is a self-delivery device, if you will, and the individual doses themselves. And they -- they take the dose that does what they want it to do. And more often than not, as a person becomes more and more dependent or addicted to nicotine, a lot of the doses they use are to avoid withdrawal symptoms, and that's why patients are -- for the patients that we see, that is probably one of the most compelling forces and the reason that they continue to use and use high levels, is because they're trying to avoid withdrawal symptoms.

Q. Please continue, doctor.

A. Okay. So I think we're through with the lung tutorial. And then we'll go to the heart and just show you how --

A lot of this is repetitious, and I hope I'm not being too repetitious, but it is important for all of us to understand how these are -- these drugs are handled in the system.

So now we've taken away the outside and we're going to look mainly at the way the heart and the lungs interact. And again I'll be repeating some

things, but -- but that's Okay. When we look here at the inferior vena cava -- and we abbreviate that IVC -- and we have the superior vena cava up here, again, bringing blood from the limbs and from the head and from the -- and in the case of the inferior vena cava, coming from the lower part of the body, coming into the right atrium, which is here, into the right ventricle, and then pumped via the pulmonary artery into the lungs, and then gas exchange takes place out here, and then once the gas exchange takes place and the blood becomes oxygenated again, then it

goes back through the pulmonary vein into the left side of the heart, the left atrium and the left ventricle.

Now the two sides of the heart -- the right ventricle is a pumping chamber, but the pump itself doesn't have to pump very far, so it's a very thin muscle. It doesn't have to be very powerful because it's only pumping blood from here into the lungs. And there's not much resistance in the lungs unless you have emphysema, which would cause an increase in resistance in the lungs.

However, on the other side of the heart, on the -- in the left ventricle, this wall is much thicker because it's having to pump blood out through

the rest of the body, into the aorta, to the brain as well as to the rest of the body. And you can feel that in your pulse here or your pulse here. It's very pulsatile, very forceful pumping coming from the left ventricle. This is what gives you your blood pressure, the pumping from the left ventricle. The harder it pumps, the higher the pressure goes.

And this will just show the movement of blood through these vessels as it -- as it works. And it works in concert; the right side and left side are synchronized so they're pumping at the right interval and they're synchronized so the blood actually does flow through the way it's supposed to.

And this will be just a realtime, regular movement through that same scheme so you can kind of see how this works. Again about 70 beats per minute.

Okay?

Q. Can you go to the brain now, doctor?

A. That's what we'll do next.

So then once the blood has been collected in here, then it goes to the brain, and again it goes through aorta and then up to the two carotid arteries, which are the major arteries that go to the brain. And a very large part of the cardiac output, then, is circulating up there because this is the

main computer and therefore the body takes care of itself by doing that.

When we cut away and look at the substance of the brain, these will be the neurons and -- and the connectors of the neurons one to another, and then there are capillaries that will be in the middle of this that we'll see how the capillaries work. And they flow through here, and there is gas exchange here just like there was gas exchange on the other end when the -- when the lungs were being oxygenated.

So this shows a capillary with the blood cells going through it, and then these are attached to nerve cells. And there are literally millions of nerve cells that are present in the brain that are -- that are associated with capillaries where they can have oxygen to be exchanged with carbon dioxide and

other waste products as it goes through the cerebrovascular circulation. And this is meant to depict that. And you'll see oxygen going out, carbon dioxide coming in.

And this just shows the same thing in realtime to show how much faster it is with the heart beating 70 times per minute and the blood circulating up to the attic.

These membranes here are also very thin so that

the gas exchange can take place, but they're not quite as thin as they are in the lungs, which are really very delicate and very fine.

Then if you were to take that same series and look at what happens in a smoker, there are some real major differences, obviously. We'll take from the top again and go and look and see what happens when -- when a person smokes a cigarette. And in this case the smoke will be a little different color.

He's slow in turning around. There he goes.

Now I've kind of gone through the anatomy here; there's no reason to do that again. So smoke inhalation works in the same way that air inhalation does, except that now the smoke particles are going out to the farthest reaches of the lungs. Depending upon how deeply a person inhales will determine how far out into the lungs the smoke will get. Some people puff on a cigarette and -- and do not deeply inhale. Their levels of nicotine in their bloodstream will be very different from those that inhale deeply, hold their breath longer. And so there is a wide variation from one smoker to the next.

Now just to speed that up a little bit so we can go to kind of the realtime how this would be. And

when you take a deeper inhalation, like when you're inhaling a cigarette, then obviously the lungs may expand further and allow the smoke to go out further into the lungs than it would be just when you were breathing air normally, because you're not usually breathing so deeply like you would be when you're smoking a cigarette.

Q. Is this again 70 beats to the --

A. This would be 70 beats per minute, right.

And then if we were to step down and go down to where the gas exchange takes place in the lungs, we'd take -- take another look at the lungs as we get down to the alveoli, which are the small air sacks. Again there are literally millions of air sacks in the lungs of the normal person, and there's a lot of reserve there.

The width of an alveoli, if you put it in terms that might be helpful for you, a point of reference, if you're thinking about this as the width of a football field and think about the aerosol particle of -- of cigarette smoke, and you actually can see

the aerosol particles when you blow them out into the air, so -- it's kind of the white -- whiteness of smoke -- if this were a football field in size, you know, 300 feet across, an aerosol particle would be

the size of a baseball. And then if you take it down one step further, a free nicotine molecule, a free base nicotine molecule would be the size of a dust particle, just to give you a point of reference.

So this is a big cavernous opening here in comparison to the aerosol, which would be baseball size, and then when you get down into the free base nicotine that goes across this membrane, it is very tiny. It's so tiny it's hard to depict it on something as small as this is.

Q. Can it go across if it's not free base?

A. No, it cannot. It goes across in the free base form.

So I told you all that so you have a point of reference for this, which we've depicted as being the nicotine as it comes down through the lungs. We haven't depicted in this the aerosol, this is just depicted as nicotine and shows it as it goes across this membrane and it's picked up by the blood.

The other thing I point out in this is we also have carbon monoxide in -- in -- that's present in cigarette smoke, and we measure that when we do -- we have patients who are smokers, we have a little machine that's called a carbon monoxide monitor, we have them blow into the machine and we can actually

look at the carbon monoxide levels in the expired air. So smokers will have very high levels of carbon monoxide and they become tolerant to that. Other people could get headaches and get sick from having those carbon monoxide levels in their bloodstreams, but smokers can become tolerant to very high levels of this. Carbon monoxide again is the gas that if the furnace isn't work right, it can be hazardous, it can be toxic, it can kill you. It's also the gas that comes out of your car exhaust.

So the free base nicotine goes across this alveolar capillary membrane, taken up by the blood, and then it takes off and goes to the brain. So the more of this that is presented to the alveoli, the higher the concentration will be going into the bloodstream. And again the surface area of the lung is very large, and when this aerosol is present in the lungs and all these little air sacks, you can get very high concentrations going to the brain. As this is an animation, it doesn't show it in detail, but it -- it makes the point about the levels that can be achieved in going to the brain.

So then if you were to speed that up and show it in realtime, just so you can kind of get a feel for that, it would look like this.

Okay? So then if we go to the next step, which is again to look at the heart and how that works, it would look like this.

So again, if you can deliver a drug to the lungs out here, the short path to the brain is here, here and out the aorta. The long path is coming in through the veins, if you were to deliver the drug intravenously, and it takes a lot longer to get from here to the brain than it does from -- from the -- from a cigarette to the brain.

And then if we go to the brain and look at the brain as far as what happens up there, this is the way it looks like. And you have to think about this as a bolus.

Q. What's a bolus?

A. Bolus is like a -- a large -- a large amount going through very rapidly all together. A bolus would be like a -- a boa constrictor that swallows a rabbit; you can kind of see it as it goes through. So it all kind of goes together. So it would actually be very similar to what I've already drawn, which is this very high spike; that would be considered a bolus. If you give an IV bolus of a drug, intravenous bolus, which is the term the nurses use and the physicians use, it would be a syringe

full, and they'd push it in as fast as they could to get it into the system faster.

So think about this different color as being the bolus of nicotine that would be coming in after a person smokes a cigarette, and it goes down -- up to the brain. After each puff there is a little bolus. Each puff will give one.

Q. Doctor, can you stop right there?

A. Sure.

Q. What are we seeing? What's the purple?

A. These are the neurons. And it's hard to depict those on an animation. And there are various shapes and sizes of neurons. The neuron body is here, but then these -- these long dendrites, if you will, will then go on down to attach to the next neuron. It's kind of like a relay system in the brain; one neuron will activate another one as it releases a neurotransmitter from one to the other until it gets to the end of the -- end of the race, if you will, and then the output from that neuron is whatever the activity is.

So those are the nerve cells. And there's some in the background. There are various different types of nerve cells. And this is the capillary, this is where the blood supply is coming.

Q. So the neurotransmitter again is the nicotine?

A. That's correct.

Q. All right.
A. That's correct. And there are a wide variety of neurotransmitters. And nicotine causes the release of a wide variety of neurotransmitters, not just dopamine. It can cause the release of other neurotransmitters like serotonin, norepinephrine, as well as a lot of other different neurotransmitters. So it has a lot of effects on the brain, but the one we focus on when we talk about a drug of addiction is in the acetylcholine receptors in the area of the brain that has to do with addictive drugs, and then the release of dopamine.
Q. Do all of these neurotransmitters activate receptors which then trigger nerve cells?
A. That's the way it works. It works basically like a relay. A neurotransmitter activates a receptor which is on the surface of an neuron, which then may be just the release of whatever the end product is, and it may be another neurotransmitter that causes a reaction, or it might be transmitting a signal to another nerve cell to then activate it to make it do something. So it's -- it can be a relay system.

And this just shows the nicotine that's in the -- in the bloodstream and as it diffuses out. And again, though, this capillary may look like it's a little bit bigger than the one in the lungs. The capillaries are very thin, and then the nicotine goes out into the cells and then causes the response. So as the nicotine then comes out into the nerve cells and attaches to the nerve cells, then it can cause activation of that nerve cell.
And this is a depiction of the nicotinic receptors. These are acetylcholine receptors, they're called nicotine receptors, and there are five pods, if you will. There are five -- you can see on this one there is one, two, three, four, five, there are five places on this receptor where nicotine or acetylcholine can land, and then once all five of these subunits are occupied, then that will activate the receptor.
Q. Doctor, let me ask one thing. What you said was acetylcholine?
A. Acetylcholine, yes. That is the -- that is the natural neurotransmitter. Nicotine is not a -- not normally present in your body, it's not a, quote, natural neurotransmitter in that sense.
Acetylcholine is the normal neuro -- neurotransmitter

that's present in the body of all humans. And that's what normally would activate these -- these receptors. And once activated, then the receptor will open up in the middle, and then that's -- that's how the activation occurs.
So just focus on this one right over here. You can see that all five spots have a nicotine molecule,

and then this middle part is opening up and that's called a channel. Now there are various types of channels. You may have heard of drugs that are calcium channel blockers, which are heart drugs, because calcium is one of the -- the ions that will cause activation of a neuron. And in fact in these, that's exactly the ion that goes through, so calcium that's present in this region as -- as an ion, once it goes through this channel, then it will activate this neuron, and the more of these receptors that are activated, the more active the neuron actually is. And in this situation we're talking about the neurons in certain areas of the brain that have to do with addictions. And the release of them after calcium goes through, the release of the next neurotransmitter is called dopamine.

The drug we mentioned earlier, I think, in one of the studies we've done, bupoprion or Zyban, is a

drug that helps to release or actually increase the release of this substance in the brain system. We think that's how it works in helping people to stop smoking. Because when a person smokes, very high levels of nicotine occur, and these high levels, as they spike into the central nervous system, cause these receptors to be activated and cause the outflow of dopamine from the receptors, and then dopamine is associated with the sensation, if you will, of pleasure and reward.

So that's basically how it works as far as the neuron is concerned. Once the neuron is activated, it sends an impulse down to the next synapse, and the synapse is where two neurons come together. And this synapse I've already kind of described to you. In the areas of the brain that we're talking about, the nucleus accumbens is where the dopamine receptors are. Dopamine is can he picked up by these little pellets, and then once these dopamine receptors are activated on this neuron, then that is the output, the behavioral output, the sensation output, if you will, of pleasure and reward. And in these areas of the brain, the nucleus accumbens, other drugs can cause the release of dopamine as well as nicotine. Nicotine is one that can do this. Cocaine and

opiates. Opiates are like heroin.

Dopamine is contained in these cells above in granules, and then they come to the surface and they are then released directly from the neurons.

And then we can just show it in a little faster time. Again the bolus, very high spikes going to the brain of nicotine, carried down to the capillary levels in the circulation. Nicotine leaves the capillaries, is released into the cellular structure surrounding the capillary, attached to the nicotinic receptors, activate them, which then sends, probably through an electrical sort of signal, but it's

biochemically mediated, it's chemically mediated into the synapse where the dopamine is released, and the end result occurs of pleasure and reward.
Q. Can we also depict, doctor, the upregulation and downregulation?
A. Sure. If you think about those neurons we just showed you in the -- in the -- in a person who's a non-smoker, they will be in the regular state. There will be -- there will be several -- probably hundreds and thousands of these neuro -- the neuroreceptors present on the surface of the brain. And this would be depicting several different varieties. These would be the ones that will be most active, the

higher affinity reacceptors, and some that are less active, but they could be stimulated by exposure to nicotine to become more like one of these, and the other ones just aren't quite going to make -- make the speed.

In a person who is a smoker, then obviously you would expect to see more of them present on the surface of the neuron, which is what this depicts, and -- and more of them in the more high affinity sort of state. They look the same as far as what their outline is, but once activated by the nicotine, then the output is, in this instance in this particular area of the area, its output is dopamine.

So what this -- what they respond to are these very high levels of nicotine that occur and are delivered most efficiently by a cigarette. When a person stops smoking, then this depicts a smoker with an upregulated set of neuroreceptors. Where there's more of them, they're more active.

This is a non-smoker. And so when a person gets back to this status, then -- then they have kind of a normal number of neuroreceptors present. The problem is that -- that they have been exposed to these very high levels of nicotine for many, many years usually. Smokers smoking a pack or two packs a day for 20 or

30 years have exposed these receptors to very high levels over a long period of time, and even though these may be now what's called downregulated, the fact that they were exposed to these very high levels of nicotine over so many exposures over time makes it so that when they maybe see something that looks like this (drawing) or something that looks like this, or maybe they have stress in their life, maybe someone's coming to visit that they didn't particularly want to have to come visit, and so they may even see this actually in a lot of different ways. So the smell of coffee, the sight of a glass of wine will then be transmitted. And so people think about the behavioral part of smoking as being something that just kind of happens. Well there -- there is a biochemical mediation of those sorts of sensations. Your eyes are attached to these parts of your brain,

so if you see something that triggers something that used to be associated with blood levels of nicotine that looked like this and also had the output of pleasure and reward, then that is a cue response or a trigger to smoke.

So those are the things we talk to the patients about so that they can understand that -- that in the future they may be faced with something like this and

they need to learn about it, because once sensitized, these neuroreceptors are very primed, waiting for these very high levels of nicotine to come along again. And once that happens, a relapse to smoking is just right around the corner.

Q. Thank you, doctor. That last part was that aspect of the program at the Mayo Clinic that deals with the behavioral treatment?

A. Well it's that the patients need to understand that we're talking about biochemical changes that have taken place over a longer period of time. That's -- that's why these other drugs that we're seeing that we're using now are -- are exciting, because they may be focused on areas of the brain where we can really help people to stop smoking in a better way than we've ever been able to do it.

The last part I just mentioned, we're now doing a study where we're using that drug over a longer period of time. Patients are receiving bupoprion, the one that produces more dopamine. We're giving it to them over a period of a year to see if we can prevent relapse.

Q. Is that a steady prescription or is it reduced over a period of time? Or how is that --

A. It's a steady prescription over the entire year.

We don't know if it works yet. That's still a clinical trial that we haven't broken the code on to know that it works.

Q. Doctor, I'd now like to move to the subject matter of pH of nicotine.

A. Okay.

Q. Something you mentioned. And you're familiar with the term "free nicotine?"

A. Correct.

Q. Okay. You've mentioned earlier that there's three types of nicotine.

A. Right.

Q. Can you describe what those are?

A. Well there are basically three types of nicotine, depending upon whether or not there is hydrogen ions attached to the nicotine molecule. And the free base nicotine has -- has none of the -- none of the hydrogen ions attached, and so it is a smaller molecule that allows it to traverse these membranes very rapidly.

Q. Can you describe for the ladies and gentlemen of the jury what is pH?

A. pH is a measure of the hydrogen ion concentration in a solution. The higher the hydrogen ion concentration, the -- actually the lower the pH,

because the pH is the negative logarithm of the hydrogen ion concentration. So an acid has a lower pH and a base has a higher pH. And neutral is seven, that's kind of in the middle. So when we -- the pH curve, if you will, though it looks like it's just up and down, it's straight, it is a logarithmic curve, so if you go from five to six, it's not just going one unit, it's going a ten-fold increase in -- in that measure. So there -- actually there's ten-fold less hydrogen ion concentration going from five to six, so that's a more basic solution.

Q. Were the defendants aware of free base nicotine?

A. Yes.

Q. Were they researching it?

A. Yes, for a very long time.

Q. Can you direct your attention, doctor, to volume one and Exhibit 13155.

A. Okay.

Q. Doctor, this is a memorandum, RJR secret memorandum entitled "IMPLICATIONS AND ACTIVITIES ARISING FROM CORRELATION OF SMOKE pH WITH NICOTINE IMPACT, OTHER SMOKE QUALITIES, AND CIGARETTE SALES."

Is this one of the documents that you've reviewed for purposes of giving your testimony here?

A. Yes, it is.

Q. And does it form part of the basis of your opinion?

A. It does.

Q. And this is a memo that was written by Claude E. Teague?

A. Yes, it is.

Q. Okay.

MR. CIRESI: Your Honor, we would offer Exhibit 13155.

MR. BERNICK: No objection, Your Honor.

THE COURT: Court will receive 13155.

MR. CIRESI: The record should reflect, Your Honor, that the document was produced in a number of different versions, and we put the complete document together from two separate documents so that it would be the most legible one, and those two document numbers were 13155 and 18181, but we're going by the number 13155. I just wanted the record to be clear on that.

THE COURT: Okay. Do the defendants have any problem with that?

MR. BERNICK: No, Your Honor. Mr. Ciresi's representation was satisfactory.

BY MR. CIRESI:

Q. Can you go, doctor, to the first chart in this

exhibit, which is entitled "pH CONCEPT AND SCALE."
A. Okay.
Q. Does this pictorially depict the pH scale that you've just talked about?
A. It does.
Q. Okay. Can you describe what is being depicted here, please?
A. Well again, this is a scale of zero to 14, and seven is in the middle, and seven is neutral and that -- that is the pH of water. So things above the line would be more alkaline, more basic, and they've given you some examples. Ammonia would be one that would be higher pH, it's more alkaline and more basic. Lemon juice, vinegar would be more acidic and so it's lower in its number. So this is a -- though it's a linear scale, it really is a logarithmic equation, so that going from a pH of five to six means that that solution is ten times more alkaline than the solution that was at five. It's not just a factor of one, it's a logarithmic scale.

So small movements on this scale, when you're measuring the acidity or alkalinity of a solution, small changes make a very large difference.

Q. Can you direct your attention, doctor -- first of all, let's look at the title page. "RJR SECRET

No. 15," the title is "IMPLICATIONS AND ACTIVITIES ARISING FROM CORRELATION OF SMOKE pH WITH NICOTINE IMPACT, OTHER SMOKE QUALITIES, AND CIGARETTE SALES." And if you would turn to page five, you will see Claude Teague, Jr.'s signature and signature line, he was a senior research person at RJR, and Dr. Murray Senkus, a carbon copy going to him, who was the research director.

If you could go, sir, to page two, please, doctor.

A. Okay.
Q. And at the top of the page it says "SMOKE pH AND 'FREE' NICOTINE.

"In essence, a cigarette is a system for delivery of nicotine to the smoker in attractive, useful form. At 'normal' smoke pH, at or below about 6.0, essentially all of the smoke nicotine is chemically combined with acidic substances, hence is nonvolatile and relatively slowly absorbed by the smoker. As the smoke pH increases above 6.0, an increasing proportion of the total smoke nicotine occurs in 'free' form, which is rapidly -- rapidly absorbed by the smoker, and believed to be instantly perceived as nicotine "kick". Chart VIII shows how proportion of 'free' nicotine increases as pH goes

higher."

First of all from a physiological standpoint, could you describe what is being stated in this

paragraph?
A. Well I think the words probably speak for themselves about as well as I can say them. When you have a compound or a -- or a -- a particle like nicotine, a molecule like nicotine, then if you put in a solution that is more acidic or more basic, it can affect the amount of free nicotine that's present. The nicotine molecule is in equilibrium with these three different forms of nicotines, and depending upon which solution it's in will determine which way that equilibrium is shifted. So the higher the pH, the equilibrium is shifted to there's more free nicotine available. Just as is said here, the higher the pH, the more free nicotine is available. And the free nicotine is very rapidly absorbed, gets across the membrane very quickly and into the circulation very quickly.
Q. And if you look down to paragraph four, "In addition to enhancing nicotine kick, increasing the pH, paren, increasing alkalinity, close paren, of smoke above about 6.0 causes other -- other changes, particularly when the increase in smoke pH is

achieved by adding ammonia to the blend."
Now did you find statements like this in other of the defendants' documents?
A. Yes. There were lots of statements like that.
Q. Were other defendants also investigating the increase of pH to create more free nicotine?
A. Yes, they were.
Q. Were other defendants also investigating the use and usage of ammonia to increase free nicotine?
A. Yes, they were.
Q. There's another statement here that says, "As smoke pH increases, in general stemmy taste, mouth irritation, flue-cured flavor and Turkish flavor are diminished, and burley flavor and character are enhanced. It should be noted, however, that if the smoke pH goes much above 7 at normal total smoke nicotine levels, the amount of 'free' nicotine becomes high, and this may cause harshness to the throat."
Now was the relative parameters, appropriate parameters of increasing pH studied by the defendants based upon your review of the defendants' documents?
A. Yes, it was.
Q. And was that true of the defendants other than RJR?

A. Yes, that's correct.
MR. CIRESI: Your Honor, I'm going to move on to another document here.
THE COURT: I think maybe we will be adjourning for the day.
Ladies and gentlemen, we'll be adjourning. Let me remind you we will reconvene tomorrow morning not at 9:30, but at 10:30 in the morning.

THE CLERK: Court stands adjourned until 10:30 tomorrow morning.

(Court recesses.)